TOTAL EXCHANGEABLE SODIUM IN NORMAL PREGNANCY AND IN PRE-ECLAMPSIA

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AN excessive retention of sodium is often held to be a primary or a contributory cause of pre-eclampsia. In many obstetric units the restriction of sodium chloride intake is regarded as an essential part of the treatment of pre-eclampsia. Some obstetricians also believe that sodium restriction throughout pregnancy may prevent pre-eclampsia. Until recently, however, no direct measurements of the body sodium in pre-eclampsia had been made.

With the advent of radioactive sodium, the so-called total exchangeable sodium can now be measured by the isotope-dilution technique. The total exchangeable sodium constitutes about 70–80% of the total sodium in the body, the remaining 20–30% (which is not readily exchangeable) being bound in an insoluble form, principally in bone (Forbes and Lewis 1956).

Several workers (Dieckmann and Pottinger 1957, MacGillivray and Buchanan 1958, Plentl and Gray 1959) have measured the total exchangeable sodium of pre-eclamptic and normal pregnant women. Their results are in many respects conflicting and difficult to interpret. Some workers have based their conclusions about the changes in total body-sodium in pregnancy and pre-eclampsia on the total exchangeable sodium expressed as mEq. per kg. body-weight. When the total exchangeable sodium is expressed in this way, it is a measure of the ratio of the total exchangeable sodium to the total body-weight, and an increase in the ratio does not necessarily imply an increase in the amount of exchangeable sodium in the body; it may equally well be the result of decrease in body-weight due to loss of body-fat. Furthermore, if the total exchangeable sodium and body-weight increase in the same proportion, then no matter how much sodium is retained there will be no change in the amount of exchangeable sodium expressed in mEq. per kg. body-weight. It is thus necessary to consider the changes in the absolute amounts of exchangeable sodium as well as any changes in the ratio of total exchangeable sodium to the total body-weight.

In previous investigations the mean total exchangeable sodium of groups of normal pregnant women has been compared with that of groups of pre-eclamptic women, one estimation only being made in each woman during pregnancy. These comparisons give no information about the initial levels of exchangeable sodium or about the changes in exchangeable sodium during pregnancy in the different groups of patients. Furthermore, though there may be significant changes in exchangeable sodium in the individual pre-eclamptic patients, there may be no difference between the mean values of groups of normal and pre-eclamptic women because of the wide variation in the amount of total exchangeable sodium of different women.

These difficulties may be overcome by making serial observations in the same women during pregnancy. If a large enough group is studied, a proportion of the women should develop pre-eclampsia.

Methods

One hundred and seven apparently healthy primigravidæ who were booked for hospital confinement before the 16th week of pregnancy, but were otherwise unselected, agreed to participate in the investigations. Their antenatal care was undertaken at a special clinic where they were seen by us. At each visit the women were weighed, the urine was tested for albumin, the blood-pressure (using the "point of muffling" to indicate the diastolic pressure) and arm circumference were measured, and a routine antenatal examination was carried out. The sphygmomanometer readings were corrected for variations in arm circumference, using the tables of Pickering (1955), adapted from Ragan and Bordley (1941), and the corrected "true" blood-pressure was recorded. This reading was used in classifying the women into groups. The women were advised to eat a well-balanced diet, but no specific advice was given on the amount of salt or carbohydrate to be taken. The women were seen monthly until the 30th week, fortnightly until the 36th week, and then weekly until delivery. Compound tablets of ferrous sulphate (*B.P.C.*) 1 twice daily and vitamin capsules (*B.P.C.*) 1 twice daily were given routinely throughout pregnancy, and the hæmoglobin was estimated at booking and at 34 weeks. Each woman was admitted to hospital for estimation of total exchangeable sodium at 16, 26, 36, and 38 weeks of pregnancy. On admission each woman was weighed, the blood-pressure was measured, and the urine was tested for albumin.

The total exchangeable sodium was estimated by the isotope-dilution technique of Miller and Wilson (1953). An exact volume of 10 ml. of normal saline containing 10 μC ^{24}Na was injected intravenously at noon on the day of admission. 18 hours were allowed for equilibration of the injected ^{24}Na. The bladder was emptied immediately before the injection, and three specimens of urine were collected: (1) noon till 6 A.M. the next day, (2) a "spot" sample from 6 A.M. to 7 A.M., and (3) a second "spot" sample from 7 A.M. to 8 A.M. During the day the women were not confined to bed and were encouraged to move around. The women were not allowed any food or fluid by mouth from 10 P.M. on the day of admission until 8 A.M. the next day.

The radioactivity of the urine samples was determined, using an annular-sample type scintillation counter, and the stable sodium was measured by means of an 'E.E.L.' flame photometer. Two estimates of the total exchangeable sodium corresponding to the two "spot" samples were made, as recommended by Miller and Wilson (1953), and the mean value was calculated.

During the investigation some women failed to come in at the appropriate time, or went into labour prematurely, and total-exchangeable-sodium measurements were, in consequence, not obtained. In addition, a discrepancy of greater than $\pm 10\%$ in the second estimate of the total exchangeable sodium as compared with the first was regarded as being outside the limits of experimental error, and the particular measurement was discarded. Any woman who had more than one missing value was not included in the final analysis of the results.

TABLE I—GROUPS OF PATIENTS

Group	Included in series	Discarded from series	Total
A: normal	27	21	48
B: "no man's land"	20	8	28
C: essential hypertension	12	4	16
D: pre-eclampsia (hypertension only)	5	0	5
E: pre-eclampsia (hypertension, with œdema and/or albuminuria)	5	1	6
Totals	69	34	103

The women were divided into three groups according to their blood-pressure readings before the 24th week:

Group A: normal.—Systolic 120 mm. Hg or below, and diastolic 80 mm. Hg or below.

Group B: "no man's land" (Browne 1958).—Systolic above 120 mm. Hg and/or diastolic above 80 mm. Hg, but systolic below 140 mm. Hg and diastolic below 90 mm. Hg (on 2 or more occasions 6 or more hours apart).

Group C: essential hypertension.—Systolic 140 mm. Hg or above and/or diastolic 90 mm. Hg or above (on 2 or more occasions 6 or more hours apart).

The diagnosis of pre-eclampsia was based on the criteria recommended by the American Committee on Maternal Welfare (1952), cited by Greenhill (1955). Accordingly pre-eclampsia was diagnosed when any of the following signs were present: (1) a blood-pressure of 140 mm. Hg systolic and/or 90 mm. Hg diastolic; (2) a rise of 30 mm. Hg systolic and/or 15 mm. Hg diastolic on 2 or more occasions, 6 or more hours apart; (3) generalised œdema; or (4) albumin in a catheter specimen of urine. We have regarded a rise to 140 mm. Hg systolic and/or 90 mm. Hg diastolic or more as significant only in patients who had a normal blood-pressure before the 24th week.

Eleven women had pre-eclampsia according to these criteria—all but one between the 34th and 38th week. This patient, who had acute pre-eclampsia at 28 weeks, was omitted in the statistical analysis of the results. When pre-eclampsia was diagnosed, the women were admitted to hospital and total exchangeable sodium was measured immediately after admission and before any treatment was given.

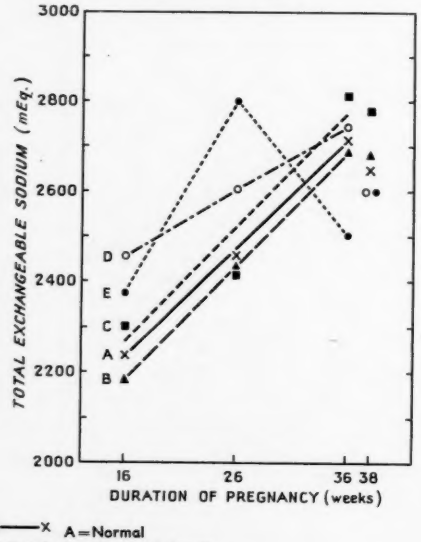

Fig. 1—Mean total exchangeable sodium at 16, 26, 36, and 38 weeks in the 5 groups of patients.

In Groups A, B, C, and D the lines shown are the calculated regression lines for the increase in total exchangeable sodium from 16 to 36 weeks.

The patients with pre-eclampsia fell into two groups:

Group D.—Those with a rise in blood-pressure only.

Group E.—Those with a rise in blood-pressure, with œdema and/or albuminuria.

The distribution of the women in the various groups and the numbers discarded for the reasons given are shown in table I; four women were omitted from the series because of abortion, severe anæmia, diabetes, and twin pregnancy.

Analysis of variance was performed on the measurements of: (1) absolute total exchangeable sodium (mEq.), (2) body-weight (kg.), and (3) total-exchangeable-sodium/body-weight ratio (mEq. per kg.) in each of the 5 groups of patients. The mean total exchangeable sodium, body-weight, and total-exchangeable-sodium/body-weight ratio at 16, 26, 36, and 38 weeks were calculated for each group. Where significant differences and highly significant differences are reported, the levels of significance are $P < 0.05$ and $P < 0.01$ respectively.

Results

Total Exchangeable Sodium

The changes in total exchangeable sodium in the five groups are shown in fig. 1 and table II.

In groups A, B, and C there was a uniform increase in the total exchangeable sodium from 16 to 36 weeks. There

TABLE II—TOTAL EXCHANGEABLE SODIUM (mEq.)

Group	Duration of pregnancy (weeks)				Error mean square	Error degrees of freedom
	16	26	36	38		
A: normal	2235	2449	2702	2649	27,431	61
B: "no man's land"	2190	2444	2695	2687	33,190	43
C: essential hypertension	2304	2420	2817	2778	24,412	26
D: pre-eclampsia (hypertension only)	2454	2607	2744	2594	12,746	10
E: pre-eclampsia (hypertension, with œdema and/or albuminuria)	2376	2797	2508	2599	68,286	9

was no significant difference between these three groups—either in the rate of increase or in the amounts of total exchangeable sodium at the different stages of pregnancy. Between 36 and 38 weeks there was a decrease in total exchangeable sodium which was, however, statistically significant only in the normal women (group A). The increase in total exchangeable sodium between 16 and 36 weeks in the normal women was 467 mEq., or approximately 23 mEq. per week.

Both groups of patients with pre-eclampsia showed significant differences from the normal. The pre-eclamptic women with a rise in blood-pressure only (group D) had a significantly greater amount of total exchangeable sodium at the 16th week. The rate of increase in total exchangeable sodium from 16 to 36 weeks in this group was significantly less than in the normal women.

In women who developed œdema and/or albuminuria as well as hypertension (group E) the total exchangeable sodium at 16 weeks did not differ significantly from that of normal women. The increase in the total exchangeable sodium in these women between 16 and 26 weeks (before the development of overt pre-eclampsia) was almost double that of normal women—421 mEq. compared with 214 mEq., the difference being statistically significant. Between 26 and 36 weeks there was a significant fall in the total exchangeable sodium in the women with pre-eclampsia (group E). This fall of 289 mEq. is in contrast to the rise of 253 mEq. found in the normal women, and the difference is highly significant. Between 36 and 38 weeks there was a rise in total exchangeable sodium, in contrast to the fall in normal women. This difference, however, was not statistically significant.

Total Body-weight

The most striking feature with regard to changes in body-weight (see fig. 2 and table III) was that women who were hypertensive at booking (group C) or who later became hypertensive (group D) were significantly heavier throughout pregnancy than normal women. The rate of gain in weight of the women with essential hypertension (group C) was significantly less than that of the normal women. There was, however, no difference between the rate of gain of weight in the women who became hypertensive during pregnancy (group D) and that in the normal women.

The mean weights of the group-B women at the different stages of pregnancy did not differ significantly from those of the normal group, though the rate of gain of weight of the women in group B was less than that of the normal women.

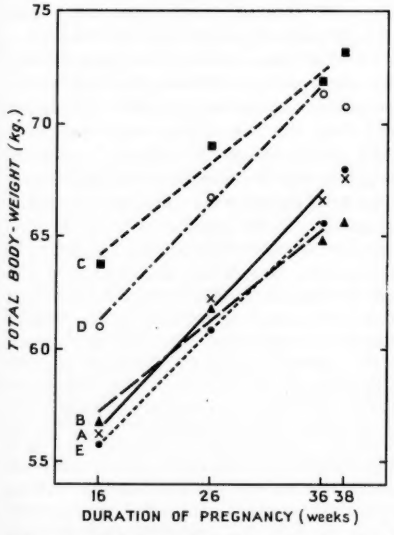

Fig. 2—Mean body-weight at 16, 26, 36, and 38 weeks in the 5 groups of patients.

The lines shown are the calculated regression lines for increase in body-weight from 16 to 36 weeks in the different groups.

The mean weights of pre-eclamptic women with œdema and/or albuminuria (group E) did not differ from those of normal women. The rate of gain in weight between 16 and 36 weeks was also similar in the two groups. Between 36 and 38 weeks, however, the normal women continued to gain weight at the previous rate, whereas the pre-eclamptic women gained weight at a significantly greater rate than before; this change took place whilst the pre-eclamptic women were in hospital under treatment.

Total-exchangeable-sodium/body-weight Ratio

In the normal women the total-exchangeable-sodium/body-weight ratio fell between 16 and 26 weeks and rose between 26 and 36 weeks (see fig. 3 and table IV); these changes were statistically significant. Between 36 and 38 weeks there was a slight fall in the total-exchangeable-sodium/body-weight ratio, but this was not significant.

At 16 weeks the group-B women had a significantly lower total-exchangeable-sodium/body-weight ratio than normal women. In contrast to the fall in the ratio between 16 and 26 weeks in the normal group there was a significant increase in the ratio in group B. During the remainder of the pregnancy there was no difference between the two groups.

TABLE III—BODY-WEIGHT (kg.)

Group	Duration of pregnancy (weeks)				Error mean square	Error degrees of freedom
	16	26	36	38		
A: normal	56·11	62·20	66·60	67·68	3·58	73
B: " no man's land " ..	56·81	61·95	64·94	65·72	2·65	54
C: essential hypertension	63·80	69·06	71·89	73·26	4·10	31
D: pre-eclampsia (hypertension only)	61·03	66·72	71·37	70·75	38·62	14
E: pre-eclampsia (hypertension, with œdema and/or albuminuria) ..	55·82	60·92	65·64	67·83	3·10	12

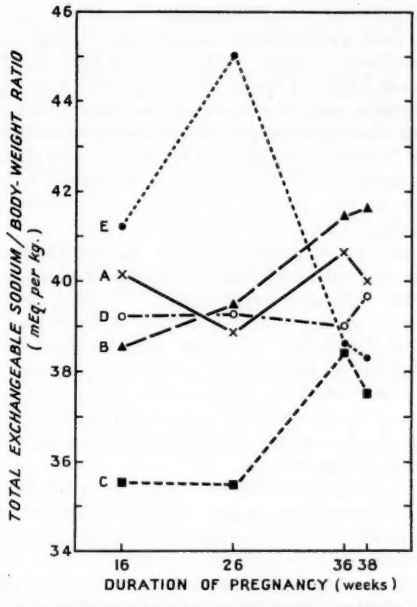

Fig. 3—Mean total-exchangeable-sodium/body-weight ratio at 16, 26, 36, and 38 weeks in the 5 groups of patients.

The sodium/body-weight ratio in the women with essential hypertension (group C) was significantly less than in the normal group at every state of the pregnancy, though the changes in the ratio were similar to those in the normal women.

TABLE IV—TOTAL-EXCHANGEABLE-SODIUM/BODY-WEIGHT RATIO (mEq. per kg.)

Group	Duration of pregnancy (weeks)				Error mean square	Error degrees of freedom
	16	26	36	38		
A: normal	40·09	38·84	40·68	40·00	4·71	61
B: " no man's land " ..	38·61	39·45	41·52	41·67	6·58	43
C: essential hypertension	36·11	35·99	38·43	37·57	4·99	26
D: pre-eclampsia (hypertension only)	39·21	39·37	39·00	39·64	3·68	10
E: pre-eclampsia (hypertension, with œdema and/or albuminuria) ..	41·21	44·99	38·60	38·29	14·96	9

The pre-eclamptic women with an increase in blood-pressure alone did not differ significantly from the normal women. But the pre-eclamptic women with hypertension, and œdema and/or albuminuria, showed decided differences. There was a significant increase in the total-exchangeable-sodium/body-weight ratio between 16 and 26 weeks, which was in contrast to the fall in the normal group. The total-exchangeable-sodium/body-weight ratio at 26 weeks was also significantly greater than that of the normal group. Between 26 weeks and the time when pre-eclampsia developed, the total-exchangeable-sodium/body-weight ratio fell markedly. This change was in contrast to the increase in the ratio in the normal women, and was again a significant one. From 36 to 38 weeks there was no significant difference in the total-exchangeable-sodium/body-weight ratio between the two groups.

Discussion

The total exchangeable sodium constitutes a major fraction (70–80%) of the total sodium in the body (Forbes and Lewis 1956). The remaining 20–30% is not readily exchangeable, and in discussing the present results it is assumed that the amount of non-exchangeable sodium remains constant throughout pregnancy. The changes in total exchangeable sodium may then be regarded as a true measure of the changes in total body-sodium during pregnancy.

On this basis, normal women gained sodium at a uniform rate between 16 and 36 weeks, the total increase being 467 mEq., or approximately 23 mEq. per week. This figure agrees closely with that of Gray and Plentl (1954) of "about 20 mEq. per week", based on serial observations in six normal pregnant women. These workers calculated that this amount could be accounted for by the normal increase in sodium in the fœtus and amniotic fluid, together with the increase in the maternal extracellular-fluid volume.

In the present investigation there was a significant fall in total body-sodium in the normal women between 36 and 38 weeks. This has not previously been reported but corresponds with a decrease in plasma-volume found at this time of pregnancy (Cope 1958) and with a decrease in the volume of amniotic fluid (Elliott 1960).

Though there was a considerable increase in the absolute amount of total exchangeable sodium in normal women between 16 and 26 weeks, there was a decrease in the ratio of total exchangeable sodium to body-weight during this period. This finding illustrates the difficulty in drawing conclusions from changes in total body-sodium expressed as mEq. per kg. body-weight without reference to the changes in the absolute amounts of body-sodium.

The changes in body-sodium during pregnancy are, presumably, the result of alterations in the sodium concentration, and/or volume, of the extracellular fluid. It must, however, be borne in mind that changes in body-fat may produce changes in the total-exchangeable-sodium/body-weight ratio. Seitchik and Alper (1956) studied the changes in total body-water in normal pregnancy and found that the increase in total body-water was greater than the gain in weight, and they inferred that there was a loss of fat during pregnancy. Such a loss of fat might account for the increase in the ratio of total exchangeable sodium to body-weight observed in the normal women between 26 and 36 weeks in the present series.

In women with essential hypertension—i.e., with a blood-pressure greater than 140 mm. Hg systolic and/or 90 mm. Hg diastolic before the 24th week—the amount of total exchangeable sodium did not differ from that in normal women. The women with essential hypertension were, however, considerably heavier throughout pregnancy and the total-exchangeable-sodium/body-weight ratio was, in consequence, smaller than that in normal women. The changes in the exchangeable-sodium/body-weight ratio during pregnancy nevertheless paralleled the changes found in normal women. This suggests that the hypertensive women were fatter than normal women but that the changes in the sodium content of the lean tissues did not differ from normal. These findings are contrary to the work of Ross (1956). Analysis of his results shows that in a group of men and non-pregnant women with essential hypertension both the absolute total exchangeable sodium and the total-exchangeable-sodium/body-weight ratio were significantly greater than the corresponding values in a normotensive control group. The patients of Ross (1956), however, had pronounced hypertension by obstetric standards, with a minimum blood-pressure of 160/100 mm. Hg.

Browne (1958) showed that women whose blood-pressures before the 24th week of pregnancy exceeded 120/80 mm. Hg, but were below 140/90 mm. Hg, had an increased fœtal mortality. In the present investigation this "no man's land" group was analysed separately (group B), but no differences from the group of normal women were found—either in the absolute amount of body-sodium or in the total-exchangeable-sodium/body-weight ratio.

In the women with pre-eclampsia characterised by hypertension and œdema and/or albuminuria, there was excessive retention of sodium (both absolutely and relatively) in the early part of pregnancy, followed by a loss of sodium by the time overt pre-eclampsia had appeared. In the only previous investigation in which serial total exchangeable-sodium estimations were made (Gray and Plentl 1954) the one woman who had pre-eclampsia showed a similar excessive increase in sodium in the period preceding the development of clinical pre-eclampsia, followed by a decrease by the time symptoms and signs of pre-eclampsia were apparent.

The findings of other workers who compared groups of normal and pre-eclamptic women are conflicting.

Dieckmann and Pottinger (1957) measured the total exchangeable sodium of normal and pre-eclamptic women before and after delivery and found that, during delivery, pre-eclamptic women showed a greater decrease in total exchangeable sodium than normal women. These workers did not state whether this difference was statistically significant or not, nor did they state the stage of pregnancy at which the antepartum estimations were made. MacGillivray and Buchanan (1958) found that there was no significant difference between the absolute amount of total exchangeable sodium of normal women in late pregnancy and that of women with pre-eclampsia. These workers did, however, find that the sodium/body-weight ratio of women with mild or severe pre-eclampsia was significantly less than that of normal women in late pregnancy—44·0 mEq. per kg. and 43·8 mEq. per kg., compared with 48·3 mEq. per kg. respectively. Plentl and Gray (1959), on the other hand, found that the total-exchangeable-sodium/body-weight ratio of women with pre-eclampsia was significantly greater than of normal pregnant women—46·0 mEq. per kg. compared with 39·6 mEq. per kg.

In the present series, when the means of the observations at 36 and 38 weeks were considered, there was no significant difference either in the absolute amount of exchangeable sodium or in the sodium/body-weight ratio between the normal and pre-eclamptic groups of women. It was only when the measurements at 36 weeks were considered in relation to the measurements at 26 and 16 weeks that the difference between normal and pre-eclamptic women became apparent. Possibly some of the differences between previous investigations are due to the total-exchangeable-sodium measurements being made at different times of pregnancy and at different stages in the development of pre-eclampsia. The present findings further suggest that there may be different types of pre-eclampsia and that abnormal changes in body-sodium may occur only in certain pre-eclamptic patients—for example, in those who have hypertension, with œdema and/or albuminuria.

The cause of the changes in body-sodium in pregnancy is not known. A progressive increase in aldosterone excretion during pregnancy has been reported by several workers (Martin and Mills 1956, Venning et al. 1957,

Jones et al. 1959) and possibly this may, in part, be responsible for the increase in total body-sodium in pregnancy. There is also evidence that the excretion of aldosterone is, in fact, decreased in women who have pre-eclampsia (Koczorek et al. 1957, Rinsler and Rigby 1957, Kumar et al. 1959) and conceivably the fall in body-sodium found in the present investigation in the pre-eclamptic patients with hypertension, with œdema and/or albuminuria, may be secondary to a decrease in aldosterone secretion. There is, however, no information about the changes in aldosterone production preceding the development of overt pre-eclampsia—i.e., when the most significant alterations in body-sodium were found in the present series.

Conclusions

The numbers of pre-eclamptic patients were small, but our findings nevertheless suggest that there is a disturbance of sodium metabolism in some patients with pre-eclampsia and that there are two phases in the development of the syndrome. There appears to be, firstly, an excessive retention of sodium in the early part of pregnancy preceding the development of pre-eclampsia, and, secondly, a loss of sodium by the time overt pre-eclampsia appears. The fall in total exchangeable sodium (which is apparent only when serial estimations are made) is contrary to the common belief that there is an excessive retention of sodium at the time that clinical pre-eclampsia develops.

The changes in body-sodium in pre-eclampsia are ill understood and are probably but a part of a complex disturbance, the nature and extent of which is, as yet, unknown. We therefore feel that the present findings do not provide grounds on which to base any hypothesis with regard to the cause of pre-eclampsia. We further feel that findings with regard to changes in total exchangeable sodium do not, in themselves, warrant any empirical attempt to "correct" the levels of body-sodium by dietary or other means.

Summary

The total exchangeable sodium has been estimated at 16, 26, 36, and 38 weeks of pregnancy in one hundred and seven primigravidæ, eleven of whom had pre-eclampsia.

The normal women showed a uniform increase in total exchangeable sodium between 16 and 36 weeks, the mean rate of increase being 23 mEq. per week.

Women with essential hypertension did not differ from normal women either in the absolute amount of total exchangeable sodium or in the changes in total exchangeable sodium during pregnancy. These women were, however, heavier than normal women and had a smaller sodium/body-weight ratio owing, presumably, to a greater proportion of fat.

The mean total exchangeable sodium of pre-eclamptic women with a rise in blood-pressure alone was significantly greater at 16 weeks than that of normal women, but the rate of gain of total exchangeable sodium during pregnancy was less.

The pre-eclamptic women who developed hypertension, with œdema and/or albuminuria, showed an excessive increase in total exchangeable sodium from 16 to 26 weeks, but a fall in total exchangeable sodium by the time signs of pre-eclampsia had appeared.

These findings suggest that in pre-eclamptic women with œdema and/or albuminuria there is an excessive retention of sodium in the early part of pregnancy, but that there is a loss of sodium by the time signs of pre-eclampsia are apparent.

We wish to thank Mr. San Bhoyroo for his careful and diligent assistance; Mrs. Daphne Harris, B.Sc., of University College, London, for help with the statistical analysis; the midwifery staff of the obstetric department of Hammersmith Hospital for their help and cooperation; and the Medical Research Council for a grant for scientific and technical assistance and equipment.

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THE DIURETIC RESPONSE TO HYGROTON, MERSALYL, AND ALDACTONE

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APPRECIATION that the therapeutic activity of diuretics is effected through sodium excretion led to a search for agents which would be more specifically natriuretics. To this end, a succession of organic substances containing the sulphamyl group has been synthesised (Sprague 1958). Some of these undoubtedly have increased potency as gauged by dose response; and, in bioassay animals, there is possible less accompanying potassium loss. Most of the assay work, however, has perforce been performed either on normal dogs, or on dogs overhydrated with saline, and there is need for direct assessment in man, in whom the pathophysiology of clinical states is more complex. In particular, this applies to the effects on potassium balance since it may well be that the liability to potassium loss after a diuretic is as much determined by the stage of the illness as by the particular diuretic employed.

There has been an increasing awareness that considerable potassium loss can sometimes take place during a therapeutic diuresis. Shaldon et al. (1960) have shown the potassium-conserving effect of a spironolactone in cirrhotics treated with chlorothiazide. The corresponding potassium-saving effect of spironolactone during hydroflumethiazide diuresis, in some patients, was demonstrated by Edmonds (1960), who also suggested that the tendency to lose potassium during diuresis was directly related to the level of activity of sodium-retaining steroids in the person concerned (Edmonds and Wilson 1960).

The assessment of diuretic effect on the human patient is fraught with difficulties, of which perhaps the greatest are: (1) the impossibility, for obvious ethical reasons, of permitting each patient to return to the baseline œdema-

laden state between individual drug stimuli; and (2) the variability which may be thereby introduced because of change in the patient's responsiveness during the period of observation. Greiner et al. (1951) advocated a creditable method for the statistical comparison of diuretics. They studied outpatients with mild congestive heart-failure, and allowed them to return to basal weight between doses, but only change of weight and variations in extent of œdema could be measured. Moreover, their observations were confined to cases of mild failure, and they were prevented from noting any difference in type of response to the diuretics employed in patients at different stages of their illness. In our own series there were all clinical grades of severity, including the advanced in whom the withholding of therapy to permit return to pretreatment levels was unjustifiable. We have attempted to compromise in our method of study of the urinary electrolyte changes with three diuretic stimuli in the individual patient using a separate control level for each diuretic—namely, the few days immediately before its administration. This device partially compensates difficulties in comparison that arise when the baseline shifts—i.e., when a responsive patient gradually approaches normal, or a deteriorating patient departs from it.

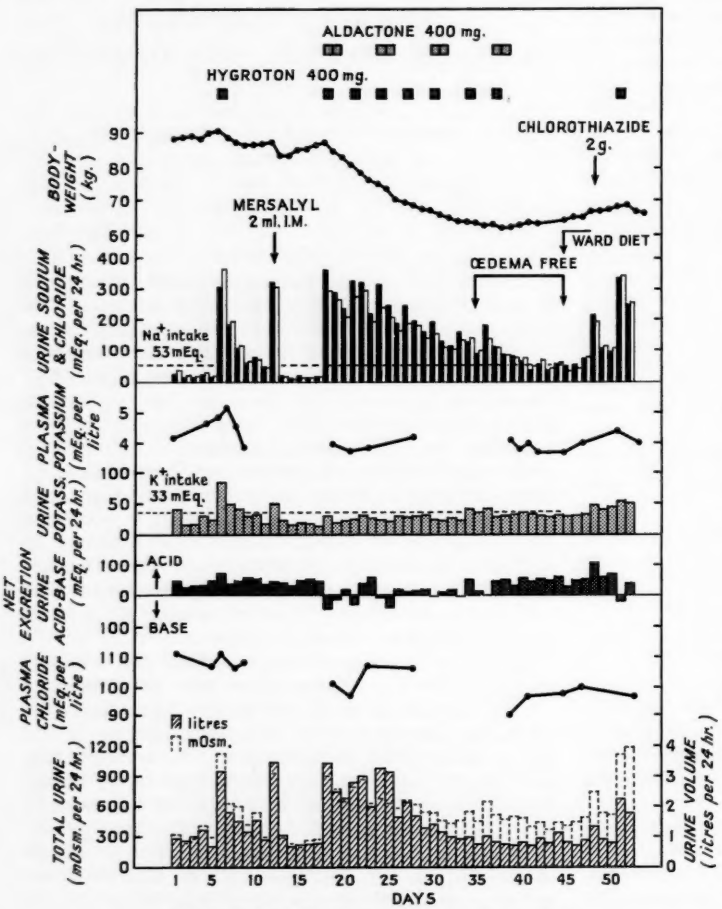
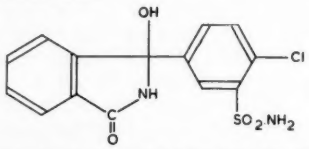


Fig. 1—Patient 10. Example of responsive patient.

Hygroton (days 6 to 8) eliminated more sodium than did mersalyl (day 12). Potassium loss was somewhat greater, but not disproportionately so, with hygroton. Aldactone reduced potassium loss from start. Kaluresis remained low, despite continued treatment with hygroton, until dietary load of potassium was altered.

The new diuretic under assessment was chlorthalidone ('Hygroton', Geigy) which is a sulphamylated isoindolin derivative: 2-chloro-5-(3-hydroxy-1-oxoisoindolin-3-yl) benzenesulphonamide.



This substance is characterised by low in-vitro carbonic-anhydrase inhibitory activity and a considerable saluretic effect in dog and man, which, after a single dose, is of several days' duration (Stenger 1959).

Methods

The plan was to compare the effects in patients admitted to hospital with generalised œdema of (1) hygroton, (2) mersalyl, and (3) hygroton given in combination with the aldosterone-antagonist spironolactone ('Aldactone').

Patients admitted with congestive heart-failure, selected to represent mild, moderately severe, and late resistant cases, comprised the larger part of the study. A patient with alcoholic cirrhosis, another with idiopathic nephrosis, and a third with gross œdema associated with necropsy-proven hepatic Hodgkin's sarcoma were also included. All were on ward low-sodium diet (about 50 mEq. sodium per day), and several received a weighed calculated diet. Those patients with cardiac failure were fully digitalised, and were receiving a maintenance dose for at least 2 weeks before this study.

After equilibration on the diet for 6 days, the first diuretic was administered; and, after 5 clear days, the second was given. Hygroton 400 mg. orally, in one dose, was employed as the first diuretic in alternate patients with 2 ml. of mersalyl given intramuscularly. These quantities were chosen as representing the probable greatest single doses of each diuretic in ordinary clinical practice.

In the second phase of the trial, which usually began 6 days after administration of the second diuretic, 400 mg. of hygroton was given at 8 A.M. at 3-day intervals. The first of these second-phase doses, and every alternate one, was accompanied by spironolactone (aldactone) 100 mg. by mouth. The aldactone was repeated at 6-hourly intervals, to a total of 800 mg., over 2 whole days.

The basic trial sequence of drugs is shown in fig. 1. Seven patients went through the complete sequence, two of them (patients 2 and 6) being given the second phase of the trial twice. Five other patients underwent the first phase only; and, of these, two did not progress to the stage of receiving hygroton combined with aldactone.

24-hour urine collections were made throughout the trial and blood-samples were taken at spaced intervals. The patients were weighed every morning, after having emptied the bladder. Sodium and potassium were determined by flame photometry, and chloride by the potentiometric method of Sanderson (1952). The Jaffé reaction was employed for urine creatinine, as a check on the completeness of collection. The net acid/base output was determined by the method of Jørgensen (1957). Osmolarity of urine was measured using a Fiske osmometer.

TABLE I—INCREASE OVER CONTROL VALUES IN URINARY ELECTROLYTE EXCRETION WITH DIURETICS

Response	Patient No.	Age	Sex	Diagnosis	Mersalyl Sodium (mEq.)	Mersalyl Potassium (mEq.)	Hygroton Sodium (mEq.)	Hygroton Potassium (mEq.)	Hygroton and aldactone Sodium (mEq.)	Hygroton and aldactone Potassium (mEq.)
Resistant	1	52	F	C.H.F., arteriosclerosis	170·1	38·8	28·1	101·4	201·7	5·0
,,	2	36	M	Alcoholic cirrhosis with ascites	227·0	142·9	109·6	287·2	802·7	60·5
,,	3	48	M	Hodgkin's sarcoma of liver with ascites	95·0	60·4	54·3	100·0	104·4	108·5
				Mean	164·0	80·7	64·0	162·9	369·6	58·0
				Standard deviation	±66·2	±55·0	±41·6	±43·4	±377·6	±51·8
Responsive	4	46	M	C.H.F., mitral disease	57·4	38·1	847·1	61·7	323·9	33·7
,,	5	64	F	C.H.F., arteriosclerosis	156·2	−4·3	249·3	43·1	94·2	−3·7
,,	6	46	M	C.H.F., cor pulmonale, diabetes mellitus	33·6	−25·3	273·2	14·7	600·2	41·4
,,	7	53	F	C.H.F., ischæmic heart-disease	108·6	16·7	363·4	42·0	547·1	75·3
,,	8	63	F	C.H.F., ischæmic heart-disease	207·6	47·5	605·9	108·1	291·8	24·1
,,	9	44	M	Nephrosis	55·4	−21·2	307·1	54·9	833·7	52·4
,,	10	49	F	C.H.F., ischæmic heart-disease	169·7	5·6	554·3	106·8	844·7	24·4
,,	11	69	F	C.H.F., cor pulmonale	−39·1	4·3	644·8	49·3	..	..
,,	12	50	M	C.H.F., ischæmic heart-disease	30·2	45·8	193·0	83·8	..	..
				Mean	86·6	11·9	448·6	62·7	505·1	35·4
				Standard deviation	±79·4	±28·8	±234·6	±32·9	±283·2	±24·8

C.H.F. = congestive heart-failure. Values given for sodium and potassium are the total outputs for each during the 72 hours following the diuretic indicated minus the total outputs during the 72 hours preceding that diuretic. The time interval between each diuretic stimulus was 6 days.

Results

In the majority of patients hygroton produced a prompt diuresis with increased excretion of sodium, chloride, and, to a lesser extent, potassium. The diuresis began within 1 or 2 hours of administration, and continued for at least 2, and often up to 6 days, after only a single dose. No instances of gastric upset, skin rash, or other ill effect attributable to the drug were observed in the 60 doses given during the trial.

A direct comparison between both sodium and potassium output produced by hygroton and by the standard 2 ml. intramuscular injection of mersalyl was undertaken. The results in the twelve patients were aggregated for each drug, and are shown in table I. The figure quoted under each heading represents the algebraic difference between the aggregate excretion during the 72 hours after (drug period), and immediately before each drug (control period).

When the series as a whole was analysed for effect of order of administration, the difference (49·0 mEq.) between the mean sodium output following mersalyl given as the first diuretic, and mersalyl given second was not sufficiently large in relation to its standard error (106·2), to be statistically significant (table II). This was also found for potassium. With hygroton, too, the order effect was unimportant.

Accordingly, in analysing the first phase of the trial, the results for the one drug were aggregated irrespective of order of administration. Initial inspection of the balance results showed a small group comprising three patients whose control levels of sodium excretion were strikingly low compared with all the others, despite their having the same low-sodium diet. Those patients with low control levels of sodium excretion were necessarily in positive balance for sodium. As a whole, they responded poorly to the several diuretic stimuli as far as weight loss or natriuresis was concerned, and all died with gross œdema soon after the end of the study. The two groups were therefore classified according to whether their control sodium excretion was above or below 30 mEq. per day. They will be termed "responsive" and "resistant" patients. The subdivision of the whole series into two groups according to level of sodium excretion during the control period was rewarding and rendered the results meaningful. The differences between the mean levels of sodium output in the three control periods in individual patients were small and not significant statistically in the two groups, but there was a difference at the $P < 0.01$ level of significance between the corresponding mean control period outputs of the two contrasted groups.

TABLE II—EFFECT OF ORDER OF ADMINISTRATION OF MERSALYL AND HYGROTON ON SODIUM AND POTASSIUM EXCRETION

—	Mean excretion increment (mEq. per 72 hours) Sodium	Potassium
Mersalyl:		
Given first, M_1	128·9	38·0
Given second, M_2	79·9	13·7
Difference, M_1–M_2	49·0	24·3
Standard error	106·2	35·6
Hygroton:		
Given first, H_1	393·9	101·6
Given second, H_2	301·4	77·9
Difference, H_1–H_2	92·4	23·7
Standard error	235·1	63·3

Five patients had hygroton first, and the remaining five in this part of the trial has mersalyl as the first diuretic.

In the larger group, the responsive patients, the natriuresis was greater with hygroton than with mersalyl (table I and fig. 1). The potassium loss with hygroton was greater, although no more potassium per unit of sodium was eliminated than with mersalyl.

In the resistant group, comparison of the sodium output during treatment with hygroton and mersalyl showed that the natriuresis was larger with mersalyl. The corresponding comparison for potassium loss showed the resistant patients to have a greater potassium loss after hygroton than after mersalyl. This increased potassium loss after hygroton was associated with a considerably reduced diuresis of sodium. In the resistant patient, mersalyl appears to be preferable to hygroton, since the latter produces less natriuresis and a disproportionately great potassium loss. This superiority of mersalyl over hygroton in resistant patients is shown in fig. 3. Potassium excretion has been drawn to twice the scale of sodium excretion to emphasise this point.

From this phase of the study, the data suggest that aldactone may have partially rectified the excessive potassium loss in resistant patients given hygroton, while enhancing the sodium excretion. These benefits were not so apparent in the responsive group in whom the potassium loss was small.

The general findings are summarised in fig. 2. Table III is a statistical treatment of the data in table I.

Effect of Prolonged Hygroton and Aldactone

In the second phase of the trial, the modifying effect of aldactone on that of hygroton was further analysed by the mathematical device of fitting a regression line with time

(Fisher and Yates 1938) separately for sodium and potassium.

An illustration is given, using the sodium data for patient 2 (fig. 4). Some such method was necessary, because of the shifting baselines of our patients—that is, whether they were responsive, and therefore in negative sodium balance, or resistant and in positive balance. The deviations between this trend, or mean excretion line and the actual 72-hour excretions after hygroton, or hygroton and aldactone were averaged for each of the two treatments in each patient; these averages, and their algebraic differences are tabulated (table IV) with the variances. If there is an even number of observations, this analytical method tends to produce a conservative estimate of the modifying effect of the aldactone.

The potassium-saving and sodium-output-increasing actions of aldactone are now seen to occur almost to the same extent in both responsive and resistant patients (table IV and fig. 5).

In these two groups, the increased excretion of sodium with aldactone in milliequivalents per 72-hour period was 142·4 and 146·7, the difference, 4·3, having a standard error of 63·6; the saving of potassium was 63·8 and 42·3, the difference of 21·5 being less than its standard error of 29·1.

Water/Solute Relation

Changes in the concentration of urine during diuresis were recorded. Intentionally the patients' natural drinking urges and supplies of fluids were not controlled or consciously modified during the trial. As a convenient index, we used the volume of water excreted per unit of osmotically active solute (millilitres per milliosmol). This water/osmolar ratio is in effect the reciprocal of concentration, larger figures expressing more dilute urines. Since the actions of the two primary diuretics (mersalyl and hygroton) were greatest during the first 24 hours after administration, the water/osmolar ratios were calculated for that period and for the 24 hours before the diuretic.

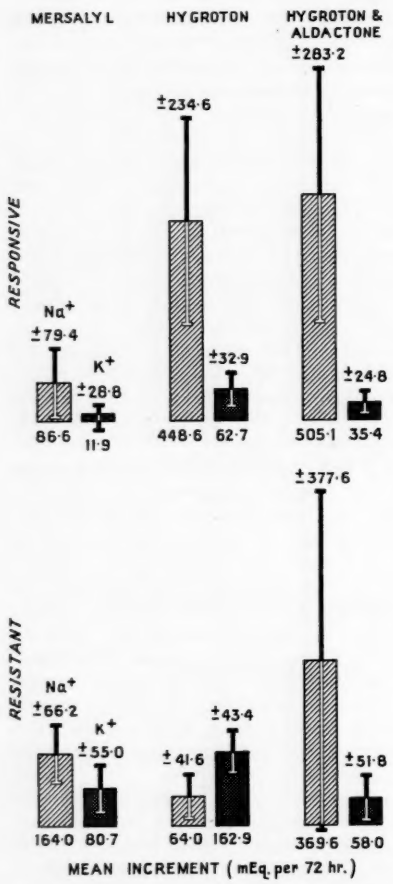


Fig. 2—The mean increments in excretion of sodium (hatched) and potassium (black) are calculated from differences in output between the 72-hour period following each diuretic and the immediately preceding 72-hour control period. Standard deviation is given with each mean.

There were 3 resistant and 9 responsive patients who received hygroton and aldactone singly. Only 7 of the responsives went on to receive hygroton combined with aldactone.

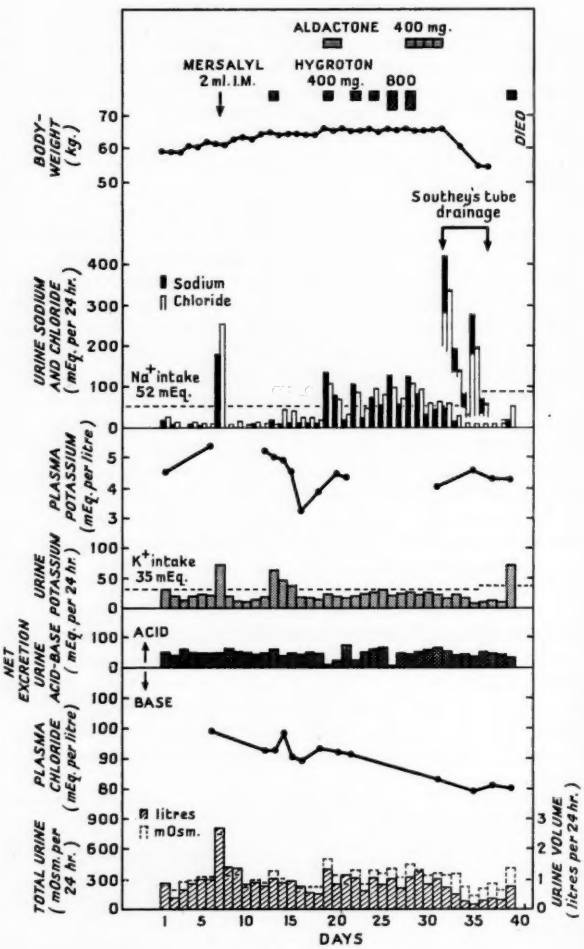


Fig. 3—Patient 2. Example of a diuretic-resistant patient.

Some sodium loss after mersalyl but an almost exclusively kaluretic response to hygroton, which response was reduced when aldactone was given with hygroton when more sodium was eliminated. Drainage by Southey's tubes was followed by oliguria and azotæmia, and the patient died. The kaluretic, without natriuretic, response recurred on day 29, the effect of aldactone having by then worn off.

The difference between these was regarded as the effect of the diuretic on water balance.

In 28 out of 34 instances, the water/osmolar ratio was higher after the diuretic. By the sign test of Steel (1959), this is statistically significant ($P < 0.01$). There was no significant difference between the increases after hygroton and those after mersalyl; but the increases were largest after hygroton and aldactone combined.

Acid/Base Changes

The net daily excretion of hydrogen ion as titratable acid plus ammonia was followed as an indirect indication of body acid/base balance. The day-to-day results in a single patient have comparative value since all were on constant diets. In most instances, the hygroton diuresis was associated with a diminution in the amount of hydrogen ion excreted daily, the alkaline swing being related roughly to the magnitude of the sodium loss. Examples are seen in fig. 1 (patient 10), when hygroton was administered alone or in combination with aldactone; and in the resistant patient 2, days 19–26 (fig. 3), after the combined diuretics were used. This effect was usual but not invariable.

Interference Between a Biguanide and Hygroton

One of our patients (no. 6) showed an unusual, but interesting, response to diuretic therapy. This patient was diabetic, with cor pulmonale. During the first part of the study he received an oral hypoglycæmic agent ('Phenformin') 25 mg. four times daily. Because of increasing ketosis with disproportionately little glycosuria, this drug was later withdrawn, and the patient given soluble insulin which restored diabetic control. There was a fairly substantial response both to hygroton, and to combined hygroton and aldactone at the beginning of the study, only 13 and 19 days after phenformin therapy had begun. Later doses of diuretics had a steadily diminishing effect, although the patient was still noticeably œdematous. On the 30th day after phenformin was started, because of lack of response to the trial diuretics, three successive aminophylline infusions were given, one accompanied by hygroton and two by mersalyl; but these likewise produced little benefit.

When hygroton was again given, 6 days after substitution of soluble insulin for phenformin, there was a prompt and characteristically prolonged diuresis, the sodium output being greater than that after the original dose of hygroton. The patient had a good response to combined aldactone and hygroton, and after three more doses of hygroton, two of them combined with aldactone, he became œdema-free.

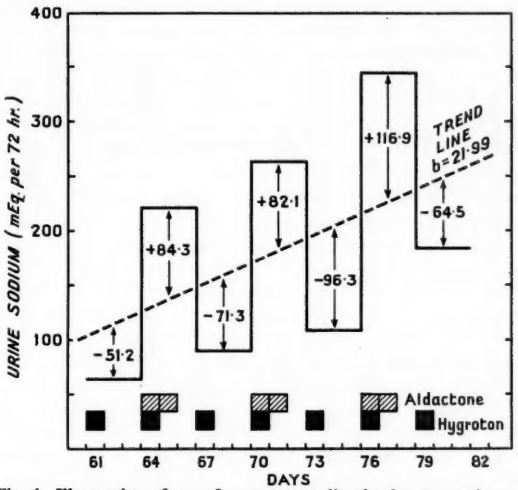


Fig. 4—Illustration of use of a regression line in the comparison of the diuretic effects of hygroton with hygroton and aldactone (patient 2b).

The actual 72-hour excretions after each drug administration are shown by the continuous line, and the deviations of these from the trend line are given; b is the regression coefficient. Table IV gives the mean excretion for each treatment and their algebraic difference, which here is +165·4. This figure is a measure of the change in sodium excretion produced by the administration of aldactone with hygroton.

Discussion

There is real difficulty in finding a reliable criterion of diuretic effect which properly allows for the prediuretic output-rate. Two criteria have commonly been used. Firstly, for a given urinary constituent, there is the increment by which the diuretic-phase excretion exceeds the

TABLE III—COMPARISONS BETWEEN RESPONSIVE AND RESISTANT GROUPS OF PATIENTS

	Mersalyl				Hygroton				Hygroton and aldactone			
	Sodium		Potassium		Sodium		Potassium		Sodium		Potassium	
	Responsive	Resistant	Responsive	Resistant	Responsive	Resistant	Responsive	Resistant	Responsive	Resistant	Responsive	Resistant
Mean increment	87·4	164·0	11·9	80·7	448·6	64·0	62·7	162·9	505·1	369·6	35·4	58·0
Difference of means	+76·6		+68·8		−384·6		+100·2		−135·5		+22·6	
P	0·2>P>0·1		0·1>P>0·05		P<0·001 significant		0·01>P>0·001 significant		0·6>P>0·5		0·6>P>0·5	

Responsive Group

	Sodium		Potassium		Sodium		Potassium		Sodium		Potassium	
	Mersalyl	Hygroton	Mersalyl	Hygroton	Hygroton	Hygroton plus aldactone	Hygroton	Hygroton plus aldactone	Mersalyl	Hygroton plus aldactone	Mersalyl	Hygroton plus aldactone
Mean increment	87·4	448·6	11·9	62·7	457·2	505·1	61·6	35·4	112·6	505·1	8·2	35·4
Difference of means	+361·2		+50·8		+47·9		−27·3		+392·5		+27·2	
P	0·001>P significant		0·01>P>0·001 significant		0·9>P>0·8		0·4>P>0·3		0·01>P>0·001 significant *		0·1>P>0·05	

Resistant Group

	Sodium		Potassium		Sodium		Potassium		Sodium		Potassium	
	Mersalyl	Hygroton	Mersalyl	Hygroton	Hygroton	Hygroton plus aldactone	Hygroton	Hygroton plus aldactone	Mersalyl	Hygroton plus aldactone	Mersalyl	Hygroton plus aldactone
Mean increment	164·0	64·0	80·7	162·9	64·0	369·6	162·9	58·0	164·0	369·6	80·7	58·0
Difference of means	−100·0		+82·2		+305·6		−104·9		+205·6		−22·7	
P	0·1>P>0·05		0·2>P>0·1		0·3>P>0·2		0·1>P>0·05		0·5>P>0·4		0·7>P>0·6	

* According to the sign test for multiple comparisons (Steel 1959) this result is not significant at the 0·05 level. The other results in this table where indicated are significant by both tests.

Two of the responsive patients (11 and 12) listed in table I did not receive the combination of hygroton and aldactone. Accordingly this comparison has been made only with the other seven cases.

The difference between the means in each comparison is calculated by subtraction of the figure on the left from the adjacent one on the right.

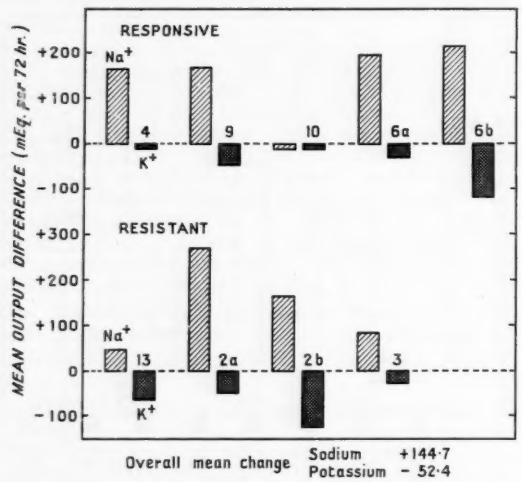


Fig. 5—The differences for each patient (indicated by number as in tables I and IV) between the mean output of sodium (hatched) and potassium (solid) during treatment with hygroton plus aldactone, and the corresponding output during treatment with hygroton alone.

The mean outputs during hygroton treatment have been regarded as basal and are represented by the zero line; the algebraic differences are plotted about this zero level. Both resistant and responsives show a characteristic response to aldactone after continued administration.

preceding control-period excretion. Secondly, there is the degree of augmentation of excretion over the control, expressed either in the form of a percentage increase over basal, or in slightly different form by the augmentation ratio of drug phase over the control. The augmentation ratio is affected excessively by low values of control excretion and may be misleading if the series includes a wide scatter of control levels. For this reason the former criterion was preferred and used by us.

Hygroton in the usual responsive patient appears more potent than mersalyl, but its advantage is lost in the resistant patient in whom a considerable potassium loss may be the predominant result. The simultaneous administration of aldactone reduced the undesirable kaluresis, and at the same time augmented the sodium output. This favourable effect of aldactone seemed to be greater in the resistant group. It was also shown by the responsive group after repeated administration and after the reduction in their weight with lessening of œdema.

The simplest explanation for these differences is based on the different degrees of associated hyperaldosteronism (Veyrat et al. 1959), and the independent suggestion by Edmonds and Wilson (1960) that in late generalised œdema states a natriuresis effected in the proximal tubule is converted to a kaluresis by subsequent aldosterone-conditioned exchange of sodium for potassium by the cation-exchange mechanism in the distal part of each nephron. The advantage over hygroton shown by mersalyl in the same patients, forming the resistant group, may be the result of differences in the pharmacodynamics of the two therapeutic agents. The natriuretic action of mersalyl (Kessler et al. 1958) is on the proximal nephron and, by analogy with chlorothiazide (Kessler et al. 1959, Vander et al. 1959), the action of hygroton may be ascribed to the same site. While the effect of mersalyl lasts for only 12 hours, however, the binding of hygroton by the renal tissue, demonstrated by Pulver et al. (1959), is associated with the characteristically prolonged diuretic action of hygroton. It may be that the intense but shortlived natriuresis, with resultant rapid passage of filtrate through the nephron characteristic of mersalyl, gives less opportunity for cation exchange than does the less abrupt natriuresis of hygroton which frequently is prolonged over 3 or 5 days.

Mersalyl administration is known to augment aldosterone output in those with congestive failure (Muller et al. 1956) as it does in normals (Barrter et al. 1956)—an effect generally believed to result from the induced shrinkage of extracellular fluid volume or indirectly of total body water. This stimulus to aldosterone formation would be expected to become increasingly clamant as the subject approached "dry weight". The mersalyl-enhanced high-sodium content of the renal tubules in these circumstances presumably would favour cation exchange of sodium for potassium. Presumably such a reactive increase in aldosterone formation would also explain the tendency to kaluresis noted by Veyrat et al. (1959) on

TABLE IV—EFFECT OF ADDING ALDACTONE TO HYGROTON IN REGULARLY ALTERNATING 3-DAY PERIODS

Response	Patient No.	Age	Sex	Diagnosis	Number of 3-day periods on Hygroton (H)	Hygroton plus aldactone (HA)	Sodium (mEq.) Mean deviation from trend line H (1)	HA (2)	Effect of aldactone (2)−(1)	Potassium (mEq.) Mean deviation from trend line H (1)	HA (2)	Effect of aldactone (2)−(1)
Resistant	2(a)	36	M	C.H.F., alcoholic cirrhosis with ascites	2	1	−92·7	185·2	277·9	14·6	−29·2	−43·8
„	2(b)	36	M	C.H.F., alcoholic cirrhosis with ascites	4	3	−70·9	94·5	165·4	51·5	−68·7	−120·2
„	3	48	M	Hodgkin's sarcoma of liver with ascites	2	2	−41·3	41·3	82·6	14·3	−14·3	−28·6
„	13	30	F	C.H.F., ischæmic heart-disease	2	1	−14·5	29·0	43·5	20·9	−41·7	−62·6
							Mean (resistant group)		142·4	Mean (resistant group)		−63·8
Responsive	4	46	M	C.H.F., mitral disease	2	3	−97·9	65·2	163·1	5·9	−3·9	−9·8
„	6(a)	46	M	C.H.F., cor pulmonale, diabetes mellitus	2	2	−96·4	96·4	192·8	15·5	−15·5	−31·0
„	6(b)	46	M	C.H.F., cor pulmonale, diabetes mellitus	2	2	−106·9	106·9	213·8	59·2	−59·2	−118·6
„	9	44	M	Nephrosis	2	2	−84·6	84·6	169·2	23·8	−23·8	−47·6
„	10	49	F	C.H.F., ischæmic heart-disease	3	4	3·2	−2·4	−5·6	5·6	−4·2	−9·8
							Mean (responsive group)		146·7	Mean (responsive group)		−42·3
							Mean (all patients) ..		144·7	Mean all (patients) ..		−52·4
							Standard error		29·5	Standard error		13·9
							Difference between groups		4·3	Difference between groups		21·5
							Standard error		63·6	Standard error		29·1

Study phases (a) and (b) were separated by intervals of more than two weeks.

giving hygroton to those approaching their dry weight, whether they were responsive œdema-freed patients or normal patients given the diuretic for experimental purposes. Nevertheless, it should be remembered that some workers have found the increase in urinary aldosterone after diuretics in normals and œdematous patients to be a transient one (Truniger and Siegenthaler 1960), and accordingly aldosterone-conditioned tubular mechanisms may not afford the complete explanation.

The renal sodium-retaining mechanism in the resistant patient is apparently not easily reversible by spironolactone (Kerr et al. 1958, Cejka et al. 1960). It is believed, though not absolutely established, that aldosterone acts on the distal tubule (Vander et al. 1958). Presumably the spironolactones, the most specific kidney-level aldosterone antagonists, act there also. An agent whose action is on the proximal tubule must be employed together with aldactone before the latter has much effect (Vander et al. 1959). The sodium retention of these œdema states is probably effected in an ill-understood way by the proximal tubule, and hence does not involve aldosterone primarily. The effects of the hyperaldosteronism, which admittedly is often present, are most apparent when an agent active on the proximal tubule partly reverses the excessive sodium resorption in that area.

Possibly kaluresis following therapeutic use of a diuretic is conditioned more by the stage of the patient's œdema process, and much less than thought hitherto by the particular pharmacological properties of the diuretic itself, with the exception of the rate/intensity effect already commented on in relation to mersalyl in resistant patients.

Our observations on changes in the water/solute ratio were prompted by the reports of Laragh et al. (1958) and Januszewicz et al. (1959). Under special experimental conditions during maintained water diuresis, they noted that mersalyl, in contrast to chlorothiazide, had an additional water-eliminating effect—i.e., an increase in free-water clearance. In the present series the conditions were not directly comparable since the patient's drinking habits were not consciously altered, and the only diuretics operating were the drugs given. Our conditions were closer to those of diuretics given in clinical practice. It is of interest that most patients showed a relatively greater output of water than of solute, with little difference between the different diuretics in this respect. In particular, no difference was apparent between mersalyl and hygroton, although the increase after hygroton and aldactone was greater than after hygroton alone.

The change in net body acid/base balance during diuresis was never gross and was transient. It did not lead to a recognisable systemic acid/base disturbance. The change was most pronounced in one woman (patient 11) who had cor pulmonale with a pre-existent partly-compensated extracellular respiratory acidosis and raised plasma-bicarbonate level (CO_2-combining power 31 mEq. per litre). We believe that the minimal "alkaline tide" sometimes observed after hygroton is related to the excretion of the sodium bicarbonate contained in the œdematous fraction of the extracellular fluid which is being eliminated by diuresis. The changes observed were a reduction of daily acid output of the order of 20–30 mEq. in 24 hours which would correspond to the excretion of about one or two litres of œdema fluid and its contained bicarbonate by a patient with body fluids at normal plasma hydrogen-ion concentration. This swing towards alkalinity may correspond to the inconsistent rise in urinary hydrogen-ion concentration after hydroflumethiazide, another sulphamyl diuretic, noted by Blagg (1959). We consider it unnecessary to postulate, as did Blagg, a primary inhibitory effect on carbonic anhydrase since the acid/base change corresponds in magnitude to that to be expected from the bicarbonate elimination.

Regarding our experience with hygroton in a diabetic patient, it is of interest that Goldner et al. (1960) have reported that a few diabetic patients receiving thiazide drugs (chlorothiazide, hydrochlorothiazide, or hydroflumethiazide) in the treatment of cardiovascular disease have had their diabetic state aggravated, and this is attributed to the diuretic. Hygroton did not appear to have this effect in the diabetic (patient 6) because, when this patient was given insulin instead of phenformin, subsequent administration of hygroton did not cause hyperglycæmia or ketosis. We seem to have found the reverse effect—namely, a hypoglycæmic agent which is interfering with the action of diuretics, converting a hitherto responsive patient into a resistant one. After withdrawal of the phenformin there was again a good response to the diuretic. There may be competition between phenformin and hygroton for secretion by the renal tubules, and the action of the diuretic may be partially blocked at that level by phenformin or its metabolites.

Summary

The effects of the new sulphamyl diuretic chlorthalidone ('Hygroton') have been compared in each patient with those of the same diuretic modified by simultaneous administration of spironolactone ('Aldactone') and with those of a standard dose of mersalyl. Hygroton diuresis was still in evidence, although gradually declining, usually 3, and sometimes up to 6, days after its administration. The potency of hygroton as a sodium eliminator in the responsive patient was greater than that of mersalyl; whereas in the resistant patient—in whom the disease process was presumably more advanced—mersalyl was the more effective diuretic, and certainly caused less accompanying kaluresis. As a responsive patient reached dry weight, the proportion of potassium loss compared with the accompanying sodium loss was increased by hygroton, there being a resemblance in diuretic effect between this state and that of the resistant.

Aldactone administered with hygroton was found to enhance the sodium loss and conserve potassium in the resistant patient, and also in the responsive patient approaching normality.

The results in general are consistent with the primary fault in sodium handling in congestive heart-failure being situated in the proximal tubule. The œdema is not entirely explicable by the hypothesis of secondary hyperaldosteronism with resultant sodium retention.

The action of all three diuretic stimuli was generally accompanied by a greater increase of water output than of solute as judged by the change in water/osmolar ratio. During hygroton-induced diuresis a modest reduction in daily urinary output of ammonia plus titratable acid was frequent and is attributed to elimination of the bicarbonate content of the œdema fluid. A chance finding was a possible interference by the hypoglycæmic agent, phenformin, on the action of diuretics.

We are indebted to Prof. I. G. W. Hill for permission to investigate patients under his care, to Dr. W. A. Wilson for generous help with statistics, to the Geigy Pharmaceutical Company for supplying 'Hygroton', and to Messrs. G. D. Searle for supplies of 'Aldactone'.

This research programme has been supported by a grant from the Scottish Hospital Endowments Research Trust.

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TYPE-3 ADENOVIRUS INFECTION WITH GASTROINTESTINAL SYMPTOMS

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EVERY winter or spring the general practitioner encounters outbreaks of apparently infectious disease with fever and gastrointestinal disturbances. These are often labelled " gastric flu " for want of a more specific diagnosis, and recovery is usually rapid and spontaneous. Thus viruses are often assumed to be the cause of these episodes, but laboratory confirmation is seldom obtained. In the outbreak we describe virological methods showed that a number of rather vague illnesses of this kind were associated with the same adenovirus as caused three cases of pharyngoconjunctival fever in the same families at the same time. Furthermore, it adds to the increasing evidence (Kjellén et al. 1957b, van der Veen and van der Ploeg 1958, Gardner et al. 1960) that adenoviruses may cause diarrhœal disease.

The Outbreak

During April and May, 1960, twenty-one members of five families living in nearby houses on the same street had various degrees of indisposition, with mainly gastrointestinal symptoms and, sometimes, pyrexia and conjunctivitis.

Two families were fully investigated bacteriologically and virologically. Family A comprised the parents and five children—David aged 7, Dora aged 5, John aged 4, Mary aged 2, and Joan aged 6 months. In family B were the parents and 4 sons—William aged 5, James aged 4, George aged 3, and Henry aged 2. The course of each patient's illness (except Mrs. A and Mr. B, who had only mild transient dyspeptic symptoms) is represented in the figure.

Further epidemiological information was gained from a chance visit of family B to relatives in a town 100 miles away. At this times James B was ill with diarrhœa and vomiting, and Mrs. B developed conjunctivitis. 4 days later three of the relative's children became ill—an 11-year-old boy had conjunctivitis, a 3-year-old girl had a severe bout of vomiting, and a 6-year-old boy became listless and drowsy, refusing to eat.

Clinical Features

The great variation in symptoms in different patients is readily seen from the figure, but two broad groups could be distinguished—those with gastrointestinal disease and those with an illness resembling pharyngoconjunctival fever. The syndrome in any individual was by no means clearly defined. For example, all three patients with pharyngoconjunctival fever had at some time gastrointestinal symptoms as well.

Gatrointestinal Symptoms

Abdominal discomfort, not usually amounting to colic, was the most common symptom. This was unrelated to eating or bowel movements, and often lasted several days. In some patients the discomfort disappeared for days or weeks and then recurred just as before. Others experienced short attacks of more severe colicky pain between longer episodes of milder abdominal discomfort. The colicky pains were associated with feelings of abdominal distension and the passage of flatus.

Mild diarrhœa was common. Typically two or three semifluid foul-smelling stools were passed daily, but the more severely affected children had watery diarrhœa and on occasions they were incontinent.

Vomiting.—In some children sudden vomiting during the day or night was the first indication of illness. Others vomited during the illness, but usually only once or twice. Two children vomited intermittently for longer—one for 7 days and the other for 3 days. Practically all the patients, even if they did not vomit, had intermittent nausea, and the young children showed great vagaries of appetite from day to day.

Pharyngoconjunctival Fever

Only three patients had illnesses at all like classical pharyngoconjunctival fever (Bell et al. 1955)—Mr. A, David A, and Mrs. B. In all three pharyngitis was so slight as to be hardly noticeable, and conjunctivitis was limited to the left eye. David A's conjunctivitis was mild, lasting only 3 days, but in the adults it lasted 12 and 13 days, causing severe discomfort and being associated with considerable œdema. Mr. A had fever of 100–101°F for 7 days and David A had fever of 101–103°F for 4 days. Mrs. B had only slight general disturbance.

General Symptoms

Even without obvious evidence of fever many patients had sporadic and sudden onset of severe lassitude, with the desire to lie down and sleep. Sleep was typically broken in character. Lassitude was most noticeable in children, but adults were similarly affected.

Illustrative Case-histories

Mr. A, aged 37, complained of abdominal discomfort, slight diarrhœa, and some nausea on April 15, 1960, and this continued for a week. On April 27 his left eye became red and uncomfortable, and 2 days later it was more painful and swollen, discharging a small amount of pus. Next day he also had headache, loss of appetite, fits of shivering and lassitude, and he became febrile (100°F). These symptoms persisted for about a week. On May 6 and 7 his eye and general condition seemed to be improving, though he was still very lethargic. Next day his nausea and abdominal discomfort returned, and he vomited once at 2 A.M. By May 10 he was much better, and the conjunctivitis had resolved. For a few days more he had intermittent attacks of abdominal pain and mild diarrhœa, but on May 17 he was able to return to work although he was extremely listless, depressed, and irritable for a further week.

JOHN A, aged 4, who was previously well, suddenly vomited twice during the afternoon of April 14, and refused to eat supper. For the next 5 days he had moderate diarrhœa, he was irritable, and he ate very little. Though usually a very active

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child, he periodically fell asleep during the day, even at table during a meal. By April 20 he had apparently recovered, but from May 26 to 30 he again complained of abdominal pains and loss of appetite, and he tended to fall asleep periodically during the day.

Laboratory Studies

A total of 34 specimens—29 from family A and 5 from family B—were examined virologically. 25 were stool specimens, 2 were rectal swabs, 4 were conjunctival swabs, and 3 were throat washings. In addition serum specimens were taken for antibody studies from Mr. A. at the acute stage of illness and 14 days later, during convalescence. Stool specimens, when freshly passed, were also examined bacteriologically for salmonellæ, shigellæ, and enteropathogenic serotypes of *Escherichia coli*; and conjunctival swabs from Mr. A and Mrs. B were examined for possible bacterial causes of conjunctivitis.

Each stool was homogenised to give about a 20% suspension in phosphate-buffered saline with antibiotics. The suspension was centrifuged at 3000 r.p.m. for 30 minutes, and the clear supernatant was stored at −40°C. Throat washings, obtained by gargling with phosphate-buffered saline, were centrifuged at the same speed, antibiotic was added, and the supernatant was stored at −40°C. Each specimen was later inoculated into two tubes of human thyroid-tissue culture in a medium of Earle's saline, 0·5% lactalbumen hydrolysate, 5% calf serum, and antibiotics. Conjunctival swabs were inoculated directly into human thyroid-tissue culture, either immediately or within 30 minutes of being taken. All tubes were examined regularly for 21 days for cytopathic effects before being discarded as negative. A second aliquot of any specimen not yielding virus when tested in thyroid-tissue culture was later inoculated into HeLa-cell cultures. Adenoviruses gave characteristic cytopathic effects in thyroid-tissue cultures. Isolates were identified as adenoviruses by complement-fixation, and later typed with type-specific antisera in thyroid-tissue culture. The virus titre was estimated in a number of the original specimens. The methods of culturing human thyroid-tissue, and of growing and examining adenoviruses, are described more fully elsewhere (Duncan 1960). Adenovirus antibodies in serum specimens were titrated both by complement-fixation for group antibody, and by neutralisation of type-3 virus in thyroid-tissue culture.

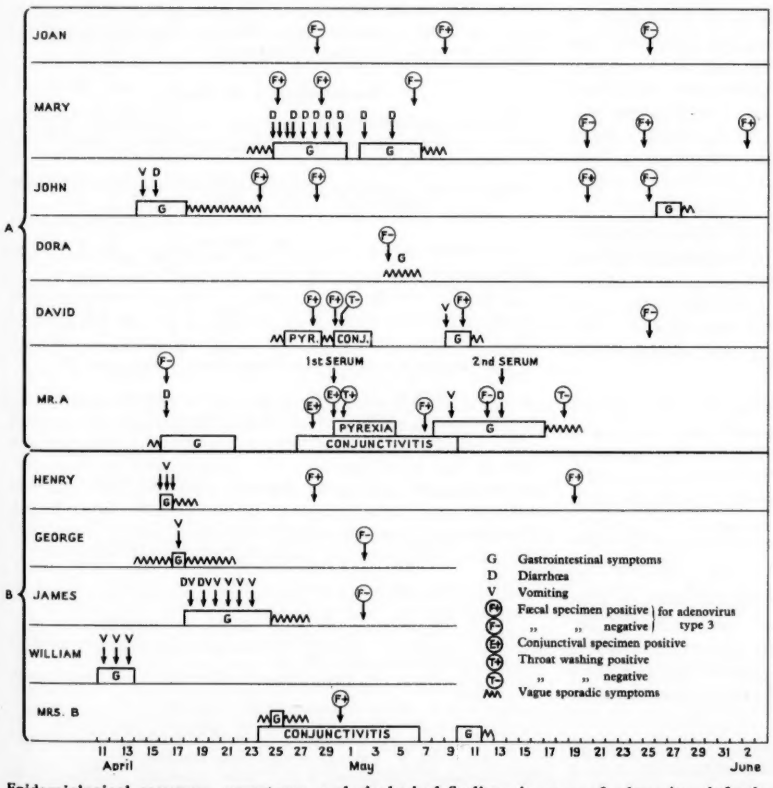
Results

No specific bacterial pathogens were cultured from the fæcal and conjunctival specimens. Adenovirus type-3 was isolated from 18 of the 34 specimens tested, and no other viruses were obtained. These were all isolated in human thyroid-tissue culture. No additional isolations were made in HeLa-cell cultures. Adenovirus type-3 was found in all 4 conjunctival swabs, in 1 of the 3 specimens of throat washings, and in 13 of the 27 stool specimens.

In the figure are details of all isolations, and of their time-relation to symptoms, for each affected member of families A and B. The virus was isolated from five of the seven members of the seven members of family A, and from some of them on 3 or 4 occasions; of the two from whom virus was not isolated, Mrs. A had no definite illness, and Dora A had only mild abdominal discomfort for 2 days. Four of the five from whom virus was isolated were ill; the fifth was the baby, Joan A, who showed no signs of illness. Fewer specimens were received from family B, and none at all from Mr. B and William B. The fæcal specimens from James B and George B, which did not yield virus, were inadequate, being rectal swabs containing very little fæcal material.

The amount of adenovirus in different specimens of fæces varied considerably. The tissue-culture-infecting dose (T.C.D.$_{50}$) of virus in different stool extracts was $10^{-1.5}$ to $10^{-5.5}$ per ml. Although the stools tended to contain more virus early in the illness than later, this was not always so. Mary A, for example, showed irregular fluctuations in the fæcal excretion of virus at different times.

A significant rise in titre of adenovirus antibodies was detected between Mr. A's serum in the acute and convalescent phases. The titre of adenovirus group complement-fixing antibodies rose from less than 1/8 to 1/32, and type-3 neutralising antibodies from less than 1/4 to 1/6.



Epidemiological sequence, symptoms, and virological findings in cases of adenovirus infection in families A and B.

Discussion

The numerous isolations of adenovirus type-3 make it quite clear that the members of families A and B were infected with this virus when they had symptoms, but this does not necessarily prove that the virus caused the symptoms. Although another agent could have been responsible, no other bacterial or viral cause was discovered. In Mr. A's case at least, it was shown by a rise in antibody titre that the acute stage of infection with adenovirus coincided with the acute symptoms of illness. If the adenoviruses had been of no ætiological significance it would probably have been possible to isolate them from healthy people and from patients with other types of illness during the same period. Stool specimens from forty-four patients with various febrile and neurological conditions were examined, without adenoviruses being isolated. We consider, therefore, that adenovirus type-3 did in fact cause these illnesses.

The first reported cases of pharyngoconjunctival fever due to adenovirus type-3 in the United States (Bell et al 1955) showed predominantly fever, pharyngitis, and conjunctivitis, gastrointestinal symptoms being noted in very few. In Britain an outbreak due to type-3 has been described (Munro-Ashman et al. 1958) in which conjunctivitis was uncommon and gastrointestinal symptoms were not encountered. Recently Bell et al. (1960) reported thirty-nine cases, six of which " either vomited or had gastrointestinal symptoms ". On the other hand, Kjellén et al (1957b) described a type-3 outbreak in Sweden in which about half the patients had gastrointestinal symptoms, and particularly abdominal pain and diarrhœa. In Holland, in an epidemic due to type-3, 21% of the patients had diarrhœa (van der Veen and van der Ploeg 1958), but the only British report of outbreak of diarrhœa definitely associated with adenoviruses was that of Gardner et al (1960), in which type-7 was incriminated.

In the present outbreak all twenty-one patients had gastrointestinal symptoms, while pharyngitis was slight, being present in only two of the three patients with conjunctivitis. Indeed, without virological investigations the outbreak would probably have been regarded as some non-specific gastric flu with a few unrelated cases of conjunctivitis. In a number of our cases the abdominal symptoms were prolonged, with intervals of remission, and it seems possible that the underlying lesion may have been mesenteric adenitis due to the virus. Adenoviruses have been isolated from mesenteric lymph-nodes in similar cases (Kjellén et al. 1957a). The interval between the arrival of family B and the onset of symptoms in the relatives whom they were visiting suggests that the incubation period may only be 4 days. This compares with an incubation period of at least 6 days found by Munro-Ashman et al. (1958). Judging from its widespread prevalence in the families investigated, and by the spread of disease with identical symptoms amongst people in the same street who were not in intimate contact with these two families, the virus seemed to be very infectious. We differ, therefore, from Bell et al. (1960) who stated that the disease is " not highly infectious "; but the age-groups in the two studies are different, and Bell et al. did not investigate apparently healthy persons.

Four of our patients were fæcal carriers of the virus when absolutely symptom-free, and in some symptoms were so mild as to have passed almost unnoticed but for their association with other cases. We incline to the view that, within the family, spread is associated with high concentrations of virus excreted in the fæces. The T.C.D.$_{50}$ of adenovirus in some stools, for example, was 10^{-6} per g. of fæces.

Finally, from the laboratory standpoint, investigation of this outbreak showed human thyroid-tissue cultures to be at least as efficient as HeLa-cell cultures for isolating adenoviruses, and we found thyroid technically much simpler to use in that it survives in perfect condition for at least 3 weeks without a change of medium.

Summary

An outbreak of diarrhœa, vomiting, and abdominal pain or discomfort involved twenty-one members of five neighbouring families. Three of the patients developed pharyngoconjunctival fever. Adenovirus type-3 was isolated from seven of the eleven members of the families who were investigated virologically.

We are grateful to Dr. C. A. C. Ross for the adenovirus complement-fixation tests, and to Mr. R. Callender for help with the figure.

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SERUM-GALACTOSAMINE

A Diagnostic Index of Liver Fibrosis in Liver Disease

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MANY studies have indicated that the level of the serum-glycoproteins may be increased in pathological conditions (Winzler 1955). Determination of the serum-glycoprotein level, however, is of limited value as an aid to diagnosis.

Recently, hexosamine, an important component of glycoprotein, has been separated into glucosamine and galactosamine (Gardell 1953, Tracey 1955, Roseman and Daffner 1956), and there is a possibility that the galactosamine/glucosamine ratio may give an indication of various pathological processes.

As one of us has reported (Yoshikawa 1961), an increase in the level of liver hexosamine, which was mostly found as galactosamine, was observed during investigations on experimentally induced liver cirrhosis. An increase in the level of serum-galactosamine in this experimental condition was also found; hence liver galactosamine appears to be significantly related to serum-galactosamine in cirrhosis of the liver.

We have studied clinically the relation between fibrosis of the liver and serum-galactosamine. Our results suggest that the serum-galactosamine level is a useful index of the degree of fibrosis in liver diseases.

Material and Methods

The serum-hexosamine level by the method of Winzler (1955) and the galactosamine/glucosamine ratio by the method of Tracey (1955) were determined in 15 healthy controls, 10 patients with acute hepatitis, 7 with chronic hepatitis, and 14 with cirrhosis of the liver. Most of the patients with cirrhosis had several liver-function tests performed—icteric index, bromsulphalein retention, thymol turbidity, zinc-sulphate turbidity, and cephalin-cholesterol flocculation. Liver biopsy was done on 13 patients with liver diseases. The findings have been classified into four grades of fibrosis (Hirayama et al. 1959).

TABLE I—AVERAGE VALUES OF SERUM-HEXOSAMINE AND GALACTOSAMINE/GLUCOSAMINE RATIO IN LIVER DISEASES

Group	No. of cases	Hexosamine (mg. per 100 ml.)	Galactosamine/glucosamine ratio
Healthy controls ..	15	98 ± 3·7	0·16 ± 0·04
Acute hepatitis ..	10	136 ± 14·9	0·59 ± 0·23
Chronic hepatitis ..	7	121 ± 31·0	0·55 ± 0·40
Liver cirrhosis ..	14	149 ± 15·2	1·07 ± 0·36

The figures represent the confidence limits of mean ($\alpha = 0{\cdot}05$).

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TABLE II—LIVER-FUNCTION TESTS AND GALACTOSAMINE/GLUCOSAMINE RATIOS IN LIVER DISEASE

Diagnosis	Liver-function tests					Serum-hexosamine (mg. per 100 ml.)	Serum-galactosamine/glucosamine ratio	Grade of liver fibrosis
	Icteric index	B.S.P. (%)	Thymol turbidity	Zinc-sulphate turbidity	Cephalin-cholesterol			
Acute hepatitis	72	..	2·7	11·5	3	120	0·16	0
Acute hepatitis	90	..	1·2	5·5	0	144	0·56	0
Chronic hepatitis	11	14·0	1·5	9·1	..	172	0·19	1
Liver cirrhosis	9	28·4	9·9	25·0	1	159	0·30	1
Chronic hepatitis	7	19·2	7·6	24·1	3	167	0·34	2
Biliary cirrhosis	88	..	8·6	15·0	3	150	0·59	2
Liver cirrhosis	4	7·2	4·2	9·5	0	100	1·06	2
Liver cirrhosis	7	27·2	7·3	15·5	0	144	1·30	2
Liver cirrhosis	10	32·0	..	..	3	117	0·94	3
Liver cirrhosis	17	11·7	7·1	16·1	3	180	0·94	3
Liver cirrhosis	18	15·3	9·1	25·5	1	137	1·80	3
Liver cirrhosis	4	9·2	2·1	6·6	0	144	1·90	3
Liver cirrhosis	4	18·9	5·3	13·2	3	187	2·41	3

B.S.P. = bromsulphalein retention.

Results

Table I shows that the average normal serum-hexosamine value was $98 \pm 3{\cdot}7$ mg. per 100 ml. The galactosamine/glucosamine ratio of the serum-hexosamine was $0{\cdot}16 \pm 0{\cdot}04$. In acute or chronic hepatitis an increase in the serum-hexosamine level (especially the galactosamine component) was found. In hepatic cirrhosis, too, the level of serum-hexosamine was raised: the increase in galactosamine was outstanding, for it constituted half the hexosamine, showing that most of the increase in hexosamine was due to an increase in galactosamine.

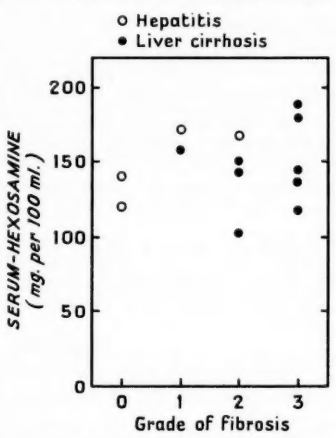

Fig. 1—Relation between serum-hexosamine and degree of liver fibrosis.

To find out the cause of the increase in the serum-galactosamine level in liver diseases, the relation between the level of serum-hexosamine (in particular that of serum-galactosamine) and liver function was investigated. Table II shows there is no definite relation between serum-hexosamine or the serum-galactosamine levels and liver-function tests.

On the other hand, some relation was found between the serum-hexosamine level and the degree of liver fibrosis (fig. 1). Moreover, there is a noticeable relation between the serum-galactosamine level and the degree of fibrosis (fig. 2); by analysis of variance, the latter correlation was statistically significant ($\alpha < 0{\cdot}05$).

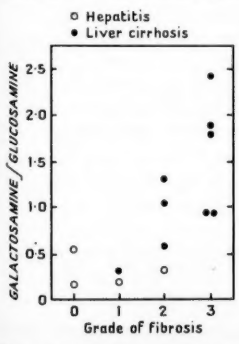

Fig. 2—Relation between serum-galactosamine and degree of liver fibrosis.

These results suggest that an increase in the serum-galactosamine level in liver diseases is due not to impaired liver function but to fibrosis.

Discussion

Little is known about the metabolism of serum-hexosamine, or even about its source. It has been suggested that serum-hexosamine may arise from depolymerisation of the ground-substance of connective tissue, from tissue proliferation, or from a general systemic response to non-specific stress (Winzler 1955, Boas et al. 1955). On the other hand, glycoprotein (particularly the seromucoid component) may be produced in the liver (Greenspan 1954), and the galactosamine/glucosamine ratio of the seromucoid may be decreased in cirrhosis (Deiss and Holmes 1958). Finally, in view of the multiplicity of the serum-glycoproteins, it has been supposed that the serum-hexosamine may have a different site of origin and may reflect different pathological processes.

An increase in the serum-galactosamine level was noted by us, not only in liver diseases, but also in almost any pathological condition (Hirayama and Yoshikawa 1960), so probably a general increase in the serum-hexosamine level denotes an increase in the amount of galactosamine.

Because of an increase in the level of galactosamine in the liver as well as in the serum in liver diseases, particularly in experimental cirrhosis of the liver, there may be a direct relation between the hexosamine of the liver and that of the serum. In these pathological conditions, the liver is probably the most active organ in the production of hexosamine. Another possibility is that an increase in the serum-galactosamine level in liver diseases—whether the galactosamine arises from the liver or from extrahepatic tissues—is due to the decreased galactosamine catabolism, probably in the liver. This hypothesis, however, seems less likely, because there was no definite relation between serum-galactosamine level and liver function. The turnover of serum-galactosamine and, if possible, that of liver galactosamine must be investigated further.

Summary

An increase in the level of serum-galactosamine was observed in liver diseases. This increase does not correlate with impaired liver function, but it does correlate with liver fibrosis.

These findings suggest that the serum-galactosamine level may be a useful index of the degree of liver fibrosis.

We are grateful to Prof. T. Masuya for invaluable criticism and encouragement.

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EFFECT OF FASTING ON LEVELS OF PLASMA-NONESTERIFIED FATTY ACIDS IN NORMAL CHILDREN, NORMAL ADULTS, AND OBESE ADULTS

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ONE of the major recent advances in the field of lipid metabolism has been the recognition of nonesterified fatty acids (N.E.F.A.) as agents in lipid transport and caloric supply (Dole 1956, Gordon and Cherkes 1956).

Plasma-N.E.F.A. levels vary inversely with the level of carbohydrate metabolism: the administration of insulin and glucose decreases the plasma-N.E.F.A. level, while fasting increases it (Dole 1956, Gordon and Cherkes 1956).

Findings reported here show that the extent of the rise in plasma-N.E.F.A. in fasting subjects is different in children, normal adults, and obese adults.

Methods

122 children, aged 4 months to 10 years, 30 normal adults, aged 18 to 50, and 15 obese adults, aged 18 to 60, were investigated. The obese adults were more than 25% overweight, according to Metropolitan Life Insurance Company criteria (Cecil and Loeb 1955), but were otherwise free of any metabolic disorder. All these subjects were inpatients, convalescing from benign illnesses, and they remained in bed for the duration of the test. Blood samples were taken at 8 A.M., after an overnight fast of 14 hours, in all subjects, and again after 5 hours' further fasting in 32 children and in all adults. Plasma-N.E.F.A. levels were determined by the method of Dole (1956).

Results

The plasma-N.E.F.A. levels in normal children, normal adults, and obese adults are shown in the accompanying table.

In the 122 children, after 14 hours' fasting the mean level of plasma-N.E.F.A. (699 ± 199* μEq. per litre) was significantly higher ($P < 0.001$) than that obtained in normal adults (448 ± 140 μEq.). The N.E.F.A. level increased in each of the 32 children who fasted for a further 5 hours, the mean increase of 343 ± 203 μEq. being highly significant ($P < 0.001$).

In normal adults, after 5 hours' further fasting, the N.E.F.A. level increased in 28 subjects, decreased in 1, and did not change in 1. In this group, the mean increase of 112 ± 84 μEq. per litre was also significant ($P < 0.01$) though significantly lower ($P < 0.001$) than that in children under similar conditions.

In a group of 15 obese patients, the mean plasma level after a 14-hour fast (778 ± 156 μEq. per litre) was significantly higher than that in the normal adult controls ($P < 0.001$). After 5 hours' further fasting, the plasma-N.E.F.A. levels increased in 8 subjects and decreased in 7; the mean increase of 17 ± 85 μEq. per litre was not significant.

EFFECT OF FASTING ON PLASMA-N.E.F.A. LEVELS IN NORMAL CHILDREN, NORMAL ADULTS, AND OBESE ADULTS

Group	No. of subjects	Mean plasma-N.E.F.A. levels (μEq. per litre)	
		14-hour fast	19-hour fast
Normal children	122	699 ± 199†	..
	32•	643 ± 143	986 ± 235‡
Normal adults	30	448 ± 140	560 ± 157§
Obese adults	15	778 ± 156†	795 ± 185‖

Figures following ± are standard deviations.

• 32 out of 122 children were reinvestigated after 5 hours' further fasting. Their 14-hour-fasting mean plasma-N.E.F.A. level was not statistically different from that of the original 122.

† Difference in plasma-N.E.F.A. level between normal children and normal adults, and between obese adults and normal adults, significant at the 0·1% level.

Increase in plasma-N.E.F.A. levels after prolongation of the fast significant at the 0·1% level (‡), the 1% level (§), or not significant (‖).

Discussion

The mean level of plasma-N.E.F.A. in 30 normal adults, fasted overnight for 14 hours, resembled those cited by Dole (1956).

The high values observed in children were unexpected. Age therefore seems of great importance in plasma-N.E.F.A. levels in fasted human beings.

The shift from the level in children to the lower level in adults is rather abrupt and takes place between the 10th and the 18th years of life. This conclusion is drawn from the equation of the straight regression lines calculated

* All the figures after ± are standard deviations.

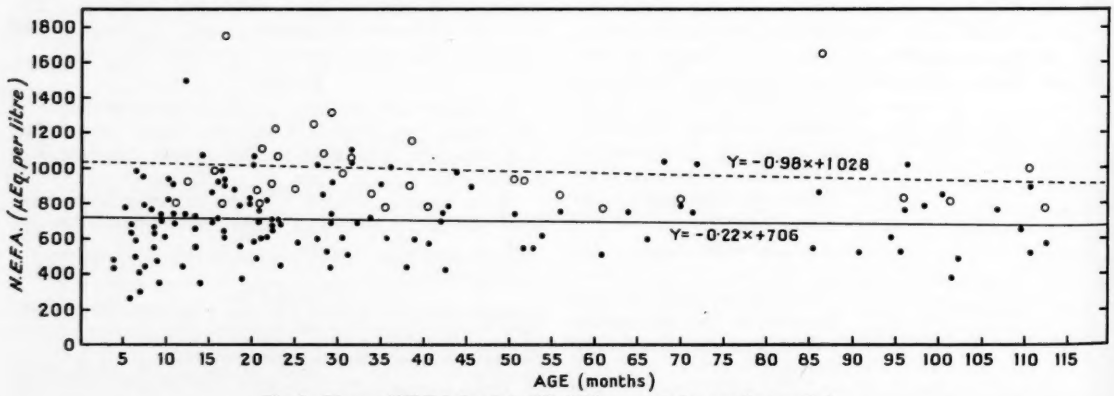

Fig. 1—Plasma-N.E.F.A. levels in 122 children related to age (in months).

• After 14 hours' fast. The equation of the straight regression line (continuous line) is $Y = -0.22X + 706$, and the regression coefficient is not significantly different from zero.

O After 19 hours' fast. The equation of the straight regression line (interrupted line) is $Y = -0.98X + 1028$, and the regression coefficient is not significantly different from zero.

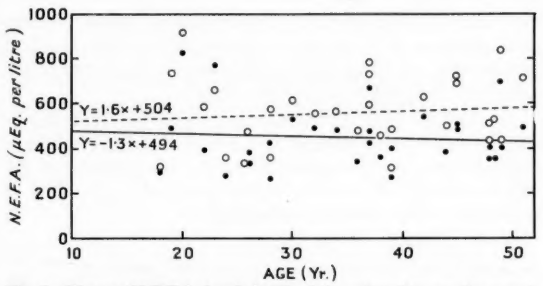

Fig. 2—Plasma-N.E.F.A. levels in 30 adults related to age (in years).

● After 14 hours' fast. The equation of the straight regression line (continuous line) is $Y=-1{\cdot}3X+494$, and the regression coefficient is not significantly different from zero.

○ After 19 hours' fast. The equation of the straight regression line (interrupted line) is $Y=1{\cdot}6X+504$, and the regression coefficient is not significantly different from zero.

when plotting the individual values of plasma-N.E.F.A. at the 14th hour of fasting against age. These equations were found to be $Y=-0{\cdot}22X+706$ in a group of 122 children (fig. 1), and $Y=-1{\cdot}3X+494$ in a group of 30 normal adults (fig. 2) (where Y represents the plasma-N.E.F.A. level in μEq. per litre and X the age in months for children and in years for adults). The regression coefficient was not statistically different from zero in either instance.

High levels of plasma-N.E.F.A. in fasted children might simply reflect the intense metabolic changes characteristic of childhood: a fast of the same duration is probably more severe in children than in adults and could result in a higher rate of production of N.E.F.A. to meet the metabolic demand. Such an explanation is not entirely satisfactory, since the basal metabolic rate is known to fall progressively with age while no such gradual decrease was observed with the plasma-N.E.F.A. levels.

A change of growth-hormone activity with age could also be involved. It is well known that the administration of growth hormone increases the plasma-N.E.F.A. level in man (Raben and Hollenberg 1959). Conversely hypopituitary patients (Perry and Gemmel 1960) and hypophysectomised monkeys (Goodman and Knobil 1959) respond to fasting with only a small rise in plasma-N.E.F.A. level. In hypopituitary patients neither steroids nor thyroid hormone can restore this response to normal (Perry and Gemmel 1960), which seems to indicate that a lack of growth hormone is specifically involved. Our finding that children respond to fasting with a great increase in plasma-N.E.F.A. may well be due to high growth-hormone activity.

To gain more insight into the dynamics of the response of N.E.F.A. to fasting, the level of plasma-N.E.F.A. was in many instances determined after a 19-hour fast as well as after a 14-hour fast. These spot checks have confirmed the greater rise of plasma-N.E.F.A. in fasted children as compared with normal adults.

The response of obese adults was in sharp contrast to that of both normal adults and normal children. As reported by Dole (1956), the value of the plasma-N.E.F.A. levels was abnormally high in the obese after an overnight fast of 14 hours; but in our study prolonging the fast did not increase this level any further. The reason for this is not known, but these data emphasise the abnormal metabolism of fatty acids in overweight adults.

Summary

The plasma level of nonesterified fatty acids (N.E.F.A.) was found to be higher in children than in adults after an overnight fast of 14 hours. Prolonging the fast for 5 hours led to a greater increase of the N.E.F.A. level in the children than in the adults.

Obese adults had a higher plasma-N.E.F.A. level than normal adults after overnight fasting. Prolonging the fast for 5 hours was not followed by any significant rise in plasma-N.E.F.A. levels.

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PNEUMOTHORAX ACCOMPANYING STAPHYLOCOCCAL PNEUMONIA IN PATIENTS TREATED WITH STEROIDS

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THOUGH it is known that staphylococcal pneumonia may be accompanied by pneumothorax, we were impressed by seeing four such cases within less than two years in patients who were receiving steroid therapy. We were also struck by the fact that the pneumothorax caused virtually no symptoms. The questions arise whether the steroid treatment may have been a contributory cause of pneumothorax, and whether it may have disguised the symptoms of pneumothorax. These questions merit attention because the two possible pathogenetic factors—staphylococcal pneumonia and steroid medication—are often operative at the same time: firstly, because patients with staphylococcal infections are often treated with steroids against infectious shock; and secondly, because staphylococcal infections are often found in patients already receiving steroid therapy.

Case-reports

Case 1.—A girl, aged 15, was referred because of symptoms suggesting disseminated lupus erythematosus—a diagnosis which was confirmed later by a positive lupus-erythematosus-cell test. Treatment with prednisone 100 mg. daily was begun. Two days later there were signs of apical pneumonia of the right lung, confirmed by X-ray examination. As culture from a pharyngeal swab grew *Staphylococcus aureus* (phage-type 77), we gave antibiotics in large doses; and added corticotrophin 40 units daily. The patient responded well and for two weeks had no complaints. Four weeks after the beginning of the steroid therapy a routine X-ray examination showed bilateral pneumothorax with a pneumatocele. Pleural drainage became necessary, and *Staph. aureus* was cultured from the pus.

Case 2.—A man, aged 23, was found to have acute porphyria with quadriplegic polyradiculitis. We started treatment with hydrocortisone 100 mg. and, later, prednisone 60 mg. daily. X-ray examination of the chest had up till now been normal, but after seven days of steroid therapy it showed bilateral infiltrations, and *Staph. aureus* (phage-type 80) was cultured from the tracheal secretions. X-ray examination sixteen days after the beginning of steroid therapy showed a valvular pneumothorax on the right side, and basal fluid. This was a quite unexpected finding as the patient had not complained of any symptoms of pneumothorax. Pleural drainage was effected; *Staph. aureus* (phage-type 80) and *Pseudomonas pyocyanea* were cultured from the pus.

Case 3.—A girl, aged $3^1/_2$ years, was gravely ill when admitted. Auscultation and radiography suggested a diagnosis of pneumonia with pleurisy on the right side. *Staph. aureus* (phage-type 52/52A/80) was cultured from pleural fluid, laryngeal secretion, blood, fæces, and sputum. We gave antibiotics and steroids—hydrocortisone 50 mg. followed by cortisone 100 mg. daily. Two weeks after the beginning of steroid treatment, at a time when the patient had neither dyspnœa nor chest pain, a radiograph showed a right-sided pneumothorax with numerous small abscesses. After a time, pneumothorax and abscesses disappeared spontaneously.

Case 4.—A girl, aged 9 years, was admitted with acute leukæmia. The patient was in a poor condition, and steroid treatment was started immediately (prednisone 40 mg. daily initially, and from the sixteenth day 100 mg. daily).

Staph. aureus (phage-type 52/52A/80) was cultured from the blood, and X-ray examination showed numerous widespread areas of infiltration in both lungs. The patient responded well to steroids, blood-transfusions, and large doses of antibiotics; and we obtained a hæmatological remission. Eleven days after the beginning of the steroid treatment, a routine X-ray showed a large pneumothorax on the right side. When the girl was questioned, she remembered having had slight dyspnœa and chest pain when she was lifted out of bed to be taken to the radiological department; there had been no symptoms of pneumothorax until that moment.

Prevalence

During the period (1958-59) in which these four cases were seen, a total of 7517 patients were admitted to the epidemic department of Blegdamshospitalet. The prevalence of pneumothorax and staphylococcal pneumonia, and the number of patients who received steroid treatment are shown in the accompanying table.

DISTRIBUTION OF PNEUMOTHORAX, STAPHYLOCOCCAL PNEUMONIA, AND STEROID TREATMENT AMONG 7517 PATIENTS ADMITTED TO THE DEPARTMENT OF COMMUNICABLE DISEASES, BLEGDAMSHOSPITALET, 1958–59

Diagnosis and treatment	No. of patients with pneumothorax	No. of patients without pneumothorax	Total
Staphylococcal pneumonia: steroid therapy	4	15	19
Staphylococcal pneumonia: no steroid therapy	0	26	26
No staphylococcal pneumonia: steroid therapy	3	197	200
No staphylococcal pneumonia: no steroid therapy	3	7269	7272
Total	10	7507	7517

Pneumothorax was common in patients with staphylococcal pneumonia, irrespective of the treatment (4 out of 45).

Pneumothorax was commoner among steroid-treated patients than among patients who did not receive steroids ($t=14{\cdot}8$).

In the steroid-treated patients, pneumothorax was commoner among patients with staphylococcal pneumonia than among patients without this disease ($t=4{\cdot}64$).

In patients who did not have staphylococcal pneumonia, pneumothorax arose more often among steroid-treated patients than among patients who did not receive steroids ($t=7{\cdot}25$).

Discussion

In children pneumothorax or pyopneumothorax is no rare complication of staphylococcal pneumonia (Forbes 1946, Bühler et al. 1958, Kringelbach and Winge 1958, Rebhan and Edwards 1960).

On the other hand, a survey of published reports has shown that pneumothorax as a complication of staphylococcal pneumonia in adult patients is rare. In a case reported by Welsh (1958) spontaneous pneumothorax took place in a 21-year-old woman with staphylococcal pneumonia who had been treated with corticotrophin for four days to combat severe intoxication.

As steroids diminish inflammatory reactions and inhibit the development of adhesions, we have wondered whether steroid therapy played any part in the development of the pneumothorax in our four patients, especially in view of a fifth case seen in the same period.

This patient was a 34-year-old man with chronic myeloid leukæmia who received steroid treatment (prednisone 30 mg. daily). He had pulmonary infiltration complicated by pneumothorax with very slight subjective symptoms. The fact that staphylococci were not shown to be the cause of his lung disease is the only point on which he differs from the rest of the group.

The possibility that steroids may be a contributory cause of pneumothorax receives little support in the literature. The case reported by Welsh (1958) is reminiscent of ours, but there are several papers on the use of corticotrophin or steroids in severe staphylococcal pneumonia (Cseley et al. 1959, Louria et al. 1959, Martin et al. 1959), none of which mentions pneumothorax as a complication. This applies also to cases where steroids—either alone or in combination with antibiotics—have been used to treat non-staphylococcal pneumonia (Wagner et al. 1956, Kass and Finland 1958).

Asthmatic patients, whose disease is often accompanied by bronchitis and emphysema, do not seem to be exposed to any increased risk of pneumothorax when treated with steroids or with corticotrophin. The possibility that the steroid therapy by itself can induce pneumothorax appears remote since this complication is not mentioned in the reports of large numbers of patients who received steroids for a chronic non-pulmonary disease. Still, the table leaves no doubt that some peculiarity in the patients in our department favours pneumothorax in those of them who are treated with steroids. It is noteworthy that four of our patients had a serious mesenchymal disease.

We cannot be certain that steroid therapy was a pathogenetic factor in our patients, but we have no doubt that it covered and disguised their symptoms of pneumothorax.

Summary

Staphylococcal pneumonia tends to be accompanied by pneumothorax, especially in children.

According to published reports, steroid therapy cannot itself cause pneumothorax. Nevertheless we found that this complication was commoner among patients who were treated with steroids than among those who were not.

Steroid medication may be a contributory cause of pneumothorax in patients with staphylococcal pneumonia.

In such patients steroid therapy can completely cover up the symptoms of pneumothorax.

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Preliminary Communication

EVALUATION OF A SPECIFIC ANTISERUM FOR SERUM-β-LIPOPROTEIN ESTIMATIONS

THE association of serum lipids with atherosclerosis has led to improvement in analytic techniques for estimation of low and high density lipoproteins. Most methods for serum-lipoprotein analyses are complex and time-consuming, and they require special equipment; hence serum-lipoprotein measurements in large population groups have been difficult and expensive.

Recently, a specific antiserum has been evolved which was used by Heiskell et al.[1] for immunochemical estimation of β-lipoproteins in small quantities of human serum. Direct measurements are made of sedimented columns of antigen-antibody precipitate in capillary tubes. With slight modification, we have evaluated this technique in our laboratories on serum specimens from normal subjects as well as patients with diabetes mellitus and atherosclerotic heart-disease. The results of immunoprecipitation were compared with electrophoretic analyses of β-lipoproteins.

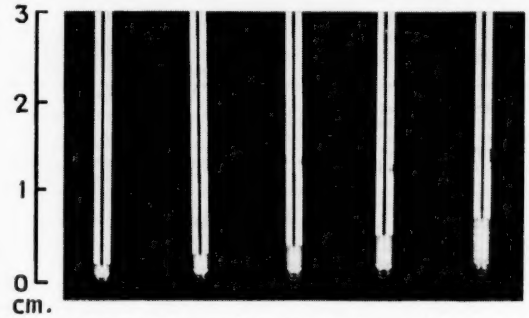

Fig. 1—Columns of β-lipoprotein precipitates ranging from 1 to 5 mm. in height.

MATERIALS AND METHODS

The standardised specific antiserum used in this study is commercially available from Hyland Laboratories, Los Angeles. The preparation is produced by immunisation of mongrel goats with ultracentrifugally isolated human β-lipoproteins of density less than 1·063 g. per ml. The antiserum appears to be specific because a single intense precipitin line corresponding to β-lipoprotein is produced by immunoelectrophoresis against pooled human serum. Aliquots of 0·06 ml. of test serum were added to 0·16 ml. of antisera on glass slides, and uniform suspensions were obtained by mixing with wooden applicator sticks. The mixtures were then drawn into capillary tubes with an inside diameter of 1·4 mm. and a total length of 75 mm. Fluid was allowed to rise in each tube by capillary action to a precalibrated point 60 mm. high. The tubes were flame sealed and then centrifuged for 5 minutes in an International microcapillary centrifuge (model MB). Columns of sedimented precipitate were measured by viewing the tubes against a millimetre scale as shown in fig. 1. Readings were made to the nearest 0·1 mm. by means of a stand magnifier.

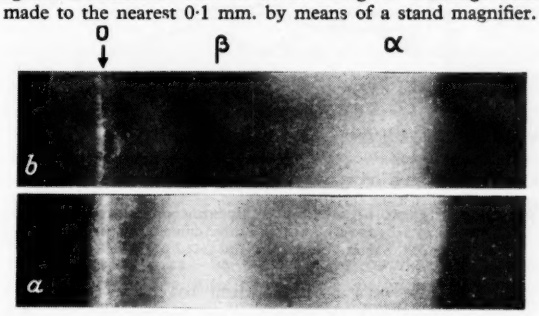

Fig. 2—Lipoprotein patterns from (*a*) a patient's serum, and (*b*) a supernatant of the patient's serum after immunoprecipitation following 16-hour electrophoretic separation on filterpaper in a Durrum-type cell using barbitone buffer (pH 8·6, ionic strength 0·075).

Aliquots of the same serum were also separated electrophoretically on filterpaper according to a technique already described.[2] α and β lipoprotein areas were identified on serum-electrophoretic strips by staining with an acid solution of protoporphyrin.[3] α and β lipoprotein cholesterol was later eluted directly from stained strips placed in glacial acetic acid saturated with ferrous sulphate.[4] After addition of concentrated sulphuric acid, cholesterol was colorimetrically measured in the eluates using a Coleman spectrophotometer at 490 mμ.[5]

RESULTS AND DISCUSSION

The efficiency of the immunochemical precipitation of β-lipoproteins was studied by electrophoretically fractionating a patient's serum, the goat antiserum, and the supernatant of this serum-antiserum mixture (1/2). After separation, the lipoproteins were estimated in terms of cholesterol (see table). The goat antiserum contained about three times more α than β lipoprotein cholesterol. In contrast, the patient's serum had a preponderance of β-lipoprotein cholesterol. But the supernatant from the serum-antiserum mixture showed a lipoprotein-cholesterol distribution similar to the original goat serum. Thus, removal of β-lipoproteins from the patient's serum seemed complete. Efficiency of precipitation was also shown by comparing electrophoretic patterns from the patient's serum before and after immunoprecipitation

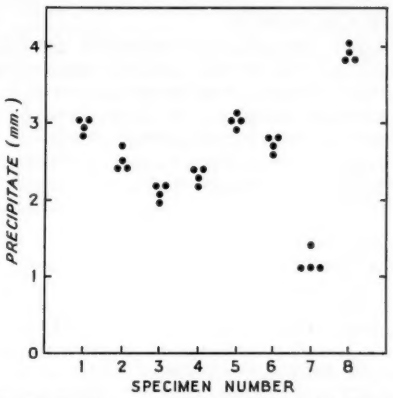

Fig. 3—Replicate immunochemical precipitations of eight randomly selected serum specimens.

1. Heiskell, C. L., Fisk, R. T., Florsheim, W., Yacki, A., Goodman, J., Carpenter, C. M. *Amer. J. clin. Path.* (in the press).

LIPOPROTEIN-CHOLESTEROL MEASUREMENTS OF SERUM, ANTISERUM, AND THE SUPERNATANT OF THE MIXTURE FOLLOWING A 16-HOUR ELECTROPHORETIC SEPARATION AT 3·0 mA IN A DURRUM-TYPE CELL USING BARBITONE BUFFER (pH 8·6, IONIC STRENGTH 0·075)

Specimen	α-lipoprotein cholesterol (mg. per 100 ml.)	β-lipoprotein cholesterol (mg. per 100 ml.)
Goat antiserum	56*	16
Patient serum	13	261
Serum-antiserum supernatant (1/2)	42 (*41*)†	14 (*11*)

* Each value represents the mean of three separate determinations.
† Figures in parentheses represent theoretical values based on a serum-antiserum dilution (1/2).

2. Searcy, R. L., Bergquist, L. M., Jung, R. C., Craig, R., Korotzer, J. *Clin. Chem.* 1960, **6**, 585.
3. Searcy, R. L., Bergquist, L. M. *Clin. chim. acta*, 1960, **5**, 940.
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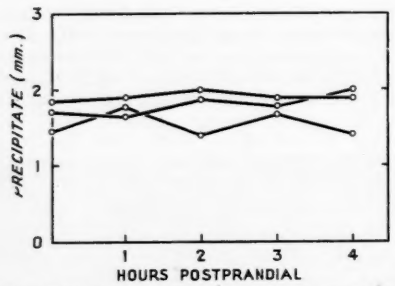

Fig. 4—The effect of alimentary lipæmia on immunochemical estimation of β-lipoproteins after a meal containing large amounts of butter, milk, bacon, fried eggs, and fried potatoes.

(fig. 2). The area corresponding to the β-lipoprotein fraction could not be detected on the protoporphyrin-stained electrophoretic strip containing the supernatant of the serum-antiserum mixture.

Reproducibility was studied by performing four separate determinations on eight randomly selected serum specimens. The mean values ranged from 1·3 to 3·9 mm. In general, the results agreed well, all measurements falling close to 10% of the mean (fig. 3).

3 healthy medical students were selected to determine the effect of alimentary lipæmia on immunochemical analysis of β-lipoproteins. Initially blood was drawn after a 12-hour fast. Each student was then given a meal containing large quantities of fat, and blood specimens were collected hourly for 4 hours. Immunochemical analysis of β-lipoproteins revealed little variation in the amounts of precipitate at the times studied (fig. 4). These data suggest, therefore, that alimentary lipæmia may have little effect on precipitation values during the first 4 hours after fat ingestion.

The amounts of β-lipoprotein precipitates (in millimetres) as determined by the immunochemical technique were compared with measurements of β-lipoproteins in terms of cholesterol on serum from 145 subjects. The test group included healthy subjects as well as hospital patients with diabetes mellitus and atherosclerotic heart-disease. A wide range of serum-β-lipoproteins was obtained

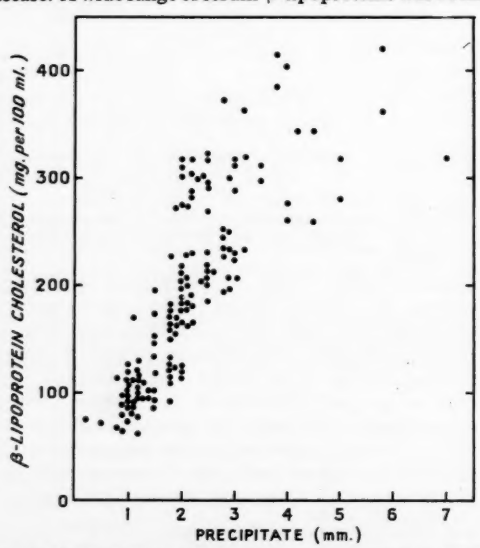

Fig. 5—Comparison of β-lipoprotein measurements in terms of cholesterol and immunochemical precipitates.

by electrophoretic and immunochemical analyses. Values yielded by the two techniques correlate within acceptable limits (fig. 5). These data suggest that in many cases, concentrations of cholesterol-containing β-lipoproteins reflect fluctuations in the total low-density-lipoprotein spectrum. We intend to make similar comparisons between electrophoretic and immunochemical estimations of high density lipoproteins.

CONCLUSIONS

A specific antiserum has been found to provide an efficient means for rapid precipitation of human serum-β-lipoproteins. Estimations of low-density lipoproteins by this technique are reproducible, and compare favourably with electrophoretic determinations. The immunochemical method may be valuable in detecting increased low-density lipoprotein levels in studies of large population groups.

This work was supported in part by grants from the American Osteopathic Association, Baxter Laboratories, and the Attending Staff Association of the Los Angeles County Osteopathic Hospital. Antiserum was generously donated by Hyland Laboratories, Los Angeles. Electrophoretic equipment was loaned by the Spinco Division of Beckman Instruments, Belmont, California.

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New Inventions

INTERMITTENT INFLATION OF ENDOTRACHEAL-TUBE CUFFS DURING POSITIVE-PRESSURE RESPIRATION

DAMAGE to the tracheal mucosa by pressure of the cuffed tracheotomy or endotracheal tube must be avoided during prolonged intermittent positive-pressure respiration. This is usually achieved by using only sufficient pressure in the cuff to prevent air leaks, and by deflating the cuff for a few breaths

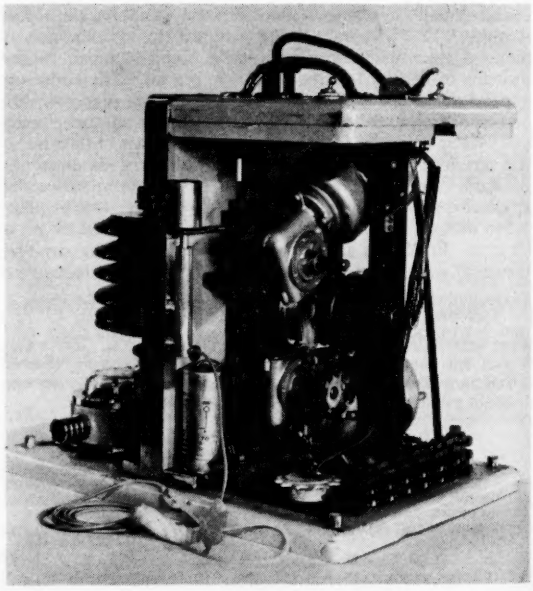

Fig. 1—General view of modification to Radcliffe respirator.

every few hours. Although this may prevent ulceration, it is far from ideal and is subject to errors, such as overdistending the cuff, omitting the periodic deflation, or even forgetting the reinflation. Similarly, cuffs which require frequent inflation because of a slow leak are a source of considerable extra work.

Except for those with bulbar palsies, most patients receiving intermittent positive-pressure respiration, including many under anæsthesia, need the cuff distended during the inflation phase of respiration only, and to this end the following addition (fig. 1) has been made to our Radcliffe respirator.

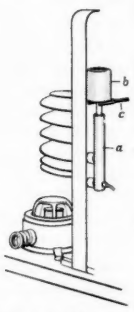

Fig. 2—Diagrammatic view of modification (explanation of letters in text).

A cylinder (12 mm. in diameter) (*a*) with a weighted piston (275 g.) (*b*) has been fitted at one side of the carriage slide (fig. 2). A fork (*c*) protrudes from the carriage so that when the latter is lifted up the piston is raised. When the weighted carriage falls, compressing the bellows, the piston also falls. The contained air is carried from the port at the bottom of the cylinder, via rubber microtubing, to the cuff of the tracheotomy tube, and distends it. When the piston is lifted up, the air is sucked out. A small hole has been drilled in the cylinder just below the piston at its highest point so that adjustment to atmospheric pressure is achieved each cycle.

With this device, overdistension is impossible (maximum volume, 5·6 c.cm.; maximum pressure, 110 mm. Hg) and the tracheal mucosa is subjected to the distension of the cuff for only about a third of the respiratory cycle, and therefore for about a third of the total time the device is used. Disasters due to a defective cuff [1] are prevented.

This system seems to have advantages over the "self-inflating" cuff [2] (the 'Mushin tube,' available from Medical and Industrial Equipment Ltd.) in that standard cuffed tubes can be used for all cases (the device need not be connected to the cuff if the latter must be inflated continuously); it is more positive in its action and is entirely independent of the inflating pressures.

This apparatus can be fitted to any mechanically driven respirator, including those used in anæsthesia, but not to gas-operated machines, without additional equipment.

This device was made in the instrument department workshop by Mr. D. McVay.

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Reviews of Books

Clinical Neurology

SIR RUSSELL BRAIN, D.M., F.R.C.P., physician to the London Hospital and the Maida Vale Hospital for Nervous Diseases. London: Oxford University Press. 1960. Pp. 400. 38*s*.

THIS book will inevitably be compared with Sir Russell's famous larger textbook. Although he describes it as different in aim and scope, many readers may regard it as a shortened version. Whether or not this is so, the book manages to give the essentials of neurology for students, residents, and practitioners in less than 400 pages. It includes valuable guides to peripheral and segmental innervation of muscles and skin. The references to electroencephalography and electromyography may perhaps be too brief to be effective. The inclusion of a brief section on psychological aspects is certainly desirable, but the account of the true meeting-place of neurology and psychiatry in the dementias associated with cerebral atrophy might have been enlarged at the expense of anxiety states, hysteria, and obsessional neurosis, which at the moment are very forced bed-fellows of neurology. Its size and the rational method of treating neurological disease as aspects of disordered physiology and anatomy will make this a useful and popular book for the student.

Throw Away Thy Rod

Living With Difficult Children. W. DAVID WILLS. London: Victor Gollancz. 1960. Pp. 148. 18*s*.

MALADJUSTED children raise difficulties out of all proportion to their numbers in the community. Their problems are usually deep-seated in origin and arise from various forms of psychological disturbance, especially from inadequacies of home life. Unfortunately there is no easy remedy and the process of rehabilitation is lengthy and expensive. But we know that without help many unhappy disturbed children will grow into maladjusted adults and, in their turn, fail as parents, so that their children will also be difficult, possibly even delinquent.

Since the war it has been the practice to provide special schools, some residential, to cope with such children. They are usually run by local education authorities, but there have also been a number of pioneer voluntary schools staffed by devoted teachers and social workers who have led the way. David Wills has been associated with such experiments for more than a quarter of a century and his name is as well known in this connection as that of George Lyward of Finchden Manor.

For the past eight years or so, Wills has been in charge of Bodenham School, a project very similar in organisation and purpose to the famous Barns School, now unhappily closed. Wills speaks quite frankly of his work as therapeutic in character. He is concerned with mental healing through environmental treatment. The boys and girls who come to live at Bodenham either for a few months or even for years are already in an advanced stage of maladjustment. Some have broken the law, others have done violence to their playmates, some are said to be beyond parental control, while others are merely retarded in mental development. The cause of these children's difficulties is usually found in their failure to achieve adequate affective relationships with their parents or siblings in early childhood. When Wills receives them their condition may be diagnosed as a deficiency of love. This has produced the indiscipline or the delinquency which are in most cases no more than the symptoms of the deeper inward malaise.

This book gives an account of what goes on at Bodenham and supplies a theoretical commentary of great interest and considerable social value. Although the ideas and methods are not new it is important that they should not be forgotten in these days when certain sections of the public are advocating a return to more punitive treatment for juvenile misfits. The difference between the delinquent and the maladjusted is, in Wills' view, largely nominal. "Some . . . happen to be caught by a policeman and take the approved school route; others . . . are 'caught' by a teacher, a parent, or a social worker and take the child-guidance route."

But the contrast between the "climate" of Bodenham and an ordinary approved school is striking. While the latter tends to use discipline and order, Bodenham emphasises self-determination and affection. One uses authority as its main technique, the other love. One offers an institution, the other a home.

Which kind of treatment is most effective with which kind of child? Should our approved schools aim to become more like Bodenham? Or should the Bodenham method be reserved for maladjusteds who have not broken the law? These are important questions that cannot be answered solely on the basis of David Wills' book. He is by nature an enthusiast, as sure of the value of love and tolerance as others are of indoctrination and the cane. The rival views can be assessed only by objective investigation, and so far there have been

few, if any, disinterested inquiries into the results achieved by either approved or maladjusted schools. Would not some independent body sponsor such research so that magistrates, administrators, and other responsible people could have the necessary guidance in their task of deciding on the best treatment for the disturbed and difficult youngsters who appear before the courts?

Resuscitation of the Newborn Infant

Editor: HAROLD ABRAMSON, M.D., professor of clinical pediatrics, New York Medical College. St. Louis: C. V. Mosby. London: Henry Kimpton. 1960. Pp. 274. 75*s*.

THE message of this book is that resuscitation of the newborn is an emergency procedure which should never be needed but if required must be carried out with expedition, skill, gentleness, and regard to the pathological physiology of the case. This outlook is correct and laudable, but it is rather indigestibly presented. The multiplicity of authors plus the desire to include everything may be responsible.

There are good discussions of the statistical, physiological, and pathological backgrounds to perinatal "anoxia" and of the events during the first minutes of life. The discussion of maternal, obstetrical, and anæsthetic factors is too synoptic to be of value. As a practical handbook of resuscitation procedures the principles discussed are helpful, but the details of apparatus are confined to those available in the U.S.A. The book is up to date, but this topicality has been bought at the price of several errors.

Helping the Partially Sighted

Correction of Subnormal Vision. NORMAN BIER, F.B.O.A., F.A.A.O., D.ORTH. London: Butterworths. 1960. Pp. 237. 50*s*.

TO the partially sighted any improvement of vision is a tremendous help, and Mr. Bier tackles this problem energetically, giving a comprehensive review of the visual aids available for patients with subnormal vision.

The book opens with two chapters on the definition of blindness and the education of partially sighted children from the optician's viewpoint. The advice is in line with medical policy —to keep borderline cases at ordinary school if at all possible. The main part of the book deals with the commonly used optical devices for subnormal vision—telescopic lenses for distance and near vision, microscopic lenses for near vision, contact lenses, magnifying glasses, and non-optical aids. These devices are clearly described in much detail and their advantages and disadvantages discussed.

The next three chapters record very fully the procedure to be followed in fitting the patient. Here some condensation and rearrangement would be an advantage and help to avoid repetition. More prominence might be given to the need for close cooperation between ophthalmic surgeon and optician at every stage in the treatment of these patients, all of whom have advanced diseases of the eye.

The book is well produced and the illustrations are exceptionally good.

Side Effects of Drugs

Unwanted Effects of Drugs as reported in the Medical Literature of the World during the period 1958–60. Compiled by L. MEYLER, M.D. London: Excerpta Medica Foundation. 1960. Pp. 239. 39*s*.

UNDESIRABLE effects of drugs are now an important cause of admission to hospital; they often prolong stay in hospital, and they may be fatal. Inquiry about drugs that have been taken is not yet firmly established in the routine of medical history-taking, and an iatrogenic illness may not be promptly recognised. Even if he is asked, the patient may not know the name or even the nature of the drugs he has taken, and the production of a box of tablets prescribed under the present regulations is usually equally unhelpful. Once suspicion has been aroused and the drug identified, this book will be of great value, particularly since it has an excellent index which includes many trade names (for example, there are 24 disguises listed under isoniazid).

This volume (the third edition) summarises the unwanted effects reported in the world's medical journals in 1958–60. It is usually particularly hard to assess accurately the toxicity to man of most therapeutic agents because in controlled clinical trials the numbers are relatively small. Toxic reactions may be apparent only when the drug becomes widely given, but by this time the extent of its use is not known nor have all the undesired effects necessarily been recorded and published. This new edition is a welcome contribution to this complicated subject.

Emotion

A Comprehensive Phenomenology of Theories and their Meanings for Therapy. JAMES HILLMAN, PH.D., director of studies at the C. G. Jung Institute, Zürich. London: Routledge & Kegan Paul. 1960. Pp. 318. 40*s*.

THIS book, based on the author's thesis, reviews the concept of "emotion" from a psychological and philosophical standpoint. After an introductory section, in which the nature of the problem and the proposed method of inquiry and integration are set out, the bulk of the book is occupied by a section subtitled Differentiation. This consists of nineteen chapters amplifying the theory of emotion through the phenomenology of theories, grouped through a wide range of types, with relevant historical background. Part three, Integration, applies the system of the four causes of Aristotle to the solution of the problem. This is a learned book, well written and readable, and the relevance of emotion to such subjects as psychotherapy and psychosomatic medicine, let alone psychiatry, should make it valuable to many physicians. It provides an anthology of current theories of emotion, and it has a good bibliography and numerous footnotes.

Clinical Applications of Diagnostic and Therapeutic Nerve Blocks

JOHN J. BONICA, M.D., director, department of anesthesiology, Tacoma General Hospital and Mountain View General Hospital. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 354. 70*s*.

THE range of application for local analgesic procedures is so great that most books on the subject are too massive for any but the expert, and tend to discourage interest in even the occasional therapeutic usefulness of nerve blocks. Dr. Bonica has therefore written this concise yet very complete account to encourage clinicians to use these techniques outside the operating-theatre. He presents clearly a very helpful collection of information and advice which contains far more than the mere description of how to perform particular nerve blocks. The book is excellently produced, but the high price may limit its impact.

Outline of Fractures (3rd. ed. Edinburgh: E. & S. Livingstone. 1960. Pp. 268. 27*s*. 6*d*.).—Within the limits implied by its title this book by Mr. John Crawford Adams is probably the best of its kind yet published. All the common bone injuries, and their complications, are here described, and all the usual methods of managing them are enumerated. But, because it is intended for the undergraduate student, there are no lengthy dissertations on the relative merits of different procedures, nor is he invited to burden his memory with practical details that are meaningless until he is actually in charge of patients. (A laudable exception is several pages on plaster-of-paris technique.) The new edition repeats the general style of the previous one, but several illustrations have been replaced by clearer examples. Those radiographs which satisfy the author's obviously strict criteria are now reproduced with a clarity that has not yet been equalled in any ordinary textbook. Indeed the only criticism which can now be made is that some readers may miss a great many scaphoid fractures if they carry in their mind's eye such a picture as he has provided.

THE LANCET

LONDON 11 MARCH 1961

Polyps et al.

ASPIRANT clinical research-workers in search of something to research into rarely escape a jocular inquiry in the vein of " why don't you investigate the relationship between hammer toes and peptic ulcer " or " hæmorrhoids and sebaceous cysts " or " rectal polyps and nasal warts ". This slender pleasantry is tolerable only until a preliminary survey of published reports reveals that a statistically significant correlation between most of these lesions has already been established. In recent years gastrointestinal polyps have been particularly liable to turn up in strange genetic company; and, considering how many of them escape detection, surprises may still be in store. The polyposes themselves can be classified into roughly three groups. The most widely recognised and best documented is familial polyposis of the colon: it may not be the commonest type, but, owing to its propensity to malignant degeneration and the feasability of total colectomy, it is of especial interest to the surgeon.[1 2] The " other " polyposis, which involves the whole of the gastrointestinal tract and the small intestine in particular, is not amenable to the same kind of radical surgery; but, associated with striking spotty pigmentation of the lips and buccal mucosa, it has risen to some fame under the name of Peutz-Jeghers syndrome.[3–6] A not inconsiderable residue, including isolated gastric polyposis or small-gut polyposis without pigmentation, fits into neither group; and the genetic status of the solitary or recurrent rectal polyps of childhood (most of which are undoubtedly inflammatory rather than neoplastic) is still not clearly defined. Any of these conditions may be associated with other inherited abnormalities, usually of connective-tissue structures; and connoisseurs of clinical oddities may relish Gardner's syndrome as a particularly picturesque combination.

Since 1953 GARDNER and his fellow-workers [7 8] have investigated over fifty members of a family afflicted with polyposis coli, multiple osteomas of the facial bones, sebaceous and epidermoid cysts, and dermoid and fibrous-tissue tumours of the skin; and a score of case-reports show that this bizarre genetic association is neither fortuitous nor exceedingly rare.[9–13] In 1937 MILLER and SWEET [14] recorded a " dermoid-type " fibrosarcoma in the abdominal scar of a woman who, two years previously, had had her colon and rectum removed on account of polyposis; and SMITH'S [15] survey of 150 Mayo Clinic patients and the valuable family studies of GORLIN and CHAUDHRY [13] suggest that polyposis and connective-tissue masses are particularly apt to run in families. Though the fibromatous component is most likely to involve laparotomy scars, tumours have also been found on the back, the chest, the neck, and the scalp, and in the mesentery: in O'BRIEN and WELLS'S [9] patient a dense fibroma was removed from the parotid region twenty years before he was treated for polyposis, and in another case COLLINS [16] noted an associated fibrosarcoma of the femur. GARDNER and his colleagues believe that many of these growths precede the polyposis; and few pathologists would state dogmatically that all of them are neoplastic. Some resemble the tumours of neurofibromatosis—another familial condition which, complete with skin nodules and café-au-lait patches, occasionally involves the gut and presents as a particularly virulent form of polyposis.[17 18] Others behave as exuberant and locally invasive scar-tissue; and, especially when they arise intraperitoneally, they probably account for some postoperative episodes of acute and subacute intestinal obstruction.

The hereditary nature of sebaceous cysts has been recognised for at least a hundred years [19]; and in 1937 MUNRO [20] referred to their possible association with intestinal cancer. The most spectacular instance of such a link has been the family described by OLDFIELD [21]; but, variously classified as " sebaceous ", " epidermoid ", or " trichoepitheliomatous ", they have also been a fairly regular feature of Gardner's syndrome.[11 13 15] Similarly, osteomas of the facial bones have been noted both as part of the complete syndrome and as isolated associated features of polyposis [7 13 22]: and osteochondromas of all kinds, clubbing of the fingers, scoliosis, and long-bone osteomata (sometimes behaving as a Brodie's abscess or as an osteoid osteoma) have been described in both polyposis coli and the Peutz-Jeghers syndrome [23–27]. Diverse as these lesions are, they by no means exhaust the list of recorded abnormalities which may be genetically related to each other and to polyps. In his original paper PEUTZ [3] spoke of " visceral " rather than of " gastrointestinal " polyposis; and bronchial, nasal, and vesical polyps have since been found in more than one family.[25 28] The occasional case of congenital heart-disease in the Peutz-Jeghers syndrome probably reflects the general lowering of the threshold of phenotypic expression which is common to many developmental abnormalities; but the genetic significance of occasional

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mental and physical retardation [29 30] and the surprisingly high incidence of ovarian abnormalities [25] are difficult to assess.

Rare though these syndromes may be, they offer common ground for investigation by geneticists, morbid anatomists, and clinicians. Their pattern of inheritance is consistent with the action of a single mutant gene or with that of several closely linked genes mutating synchronously. The working hypothesis of one gene, one enzyme is now widely accepted; and on that basis they are probably manifestations of abnormal enzyme reactions during intrauterine development. It is not unreasonable to suppose that the vast majority of our gene-enzymes are concerned with this period of intense chemical activity; and probably few retain an active metabolic role after birth. Nevertheless, it is well worth searching for persistent chemical abnormalities associated with these syndromes: the remotest glimpse into the biochemistry of fœtal differentiation would be extremely valuable. The contrast between the diversity of colonic polyps and sebaceous cysts and their presumed molecular kinship at some stage of embryonic life is a measure of our present ignorance.

If, up till now, no common chemical denominator has been uncovered, the polyposes have already shed a sidelight on the much discussed relation between genetic and environmental factors in carcinogenesis. At first it would appear that, whereas the development of a secondary carcinoma in polyposis is largely determined by a single gene and hardly at all by environmental influences, in primary cancer of the large bowel the hereditary factor is less important and almost certainly polygenic. Such a concept, however, leaves several questions unanswered; and, in particular, it does not explain the rather different behaviour of adenomatous polyps in the large and in the small intestine. DORMANDY [5 25] challenged the view that polyps in the small gut were as liable to carcinomatous degeneration as those in the colon and rectum. He pointed to the deceptive histological appearance of many surgical specimens; and he put forward the negative evidence that in most published cases and in all his own cases of the Peutz-Jeghers syndrome the clinical course belied or at least cast serious doubt on the microscopic diagnoses of small-gut malignancy. The colonic and rectal polyps, on the other hand, even though they formed part of a generalised gastrointestinal polyposis, were as liable to carcinomatous change as was polyposis coli. Large-bowel (as opposed to small-bowel) cancer remains a real danger and common cause of death in these families. (For the time being BAILEY'S [31] case of small-intestinal cancer developing in pre-existing polyps in a patient without pigmentation or a family history must be regarded as exceptional.) MORSON [32] explains the difference by classifying the small-gut polyps of the Peutz-Jeghers syndrome as hamartomas rather than as true adenomas; but, though this is an ingenious suggestion, it is odd that in gastrointestinal polyposis the small-gut polyps should behave as one and the large-gut polyps as the other. Many pathologists, moreover, find it as difficult to separate the hamartoma from the innocent adenoma as it is to distinguish between some adenomas and low-grade carcinomas. The simplest and perhaps likeliest explanation is that physical factors and the chemical and bacteriological milieu favour carcinomatous change in the large but not in the small bowel.

Unfortunately, the commonest type of gastrointestinal polyposis—polyposis coli—remains genetically "unmarked" (its linkage to the MN blood-groups awaits confirmation [33]); nor does the family pattern always conform to the textbook picture. In his detailed study of a New Zealand family VEALE [34] draws attention to the occasional late appearance of the polyps (sometimes after the age of 70). He rightly warns that "it should never be concluded that a case is a non-familial phenocopy, as this will automatically lead to a relaxation of the vigil that should be kept on descendants, possibly with tragic results". Why polyps should appear late in some and not in other members of the same family is yet another question that has still to be answered.

Mauritius and Malthus

THE developing countries all over the world face variations of the same problem. Better health means an increasing population which the existing economic system cannot support. In Mauritius last year cyclones brought matters to a head, although two investigating groups were already at work, and two recent reports [35 36] to the Governor describe the situation and suggest solutions. The position revealed is very serious. Professor TITMUSS and his associates,[36] dealing with social policies and population growth, emphasise that the island will face economic, social, and political disaster unless immediate steps are taken to reverse the present trend towards doubling the population by 1982. Professor MEADE and his team,[35] examining the economic and social structure of the island, have equally no doubt that "the future of Mauritius is at present dominated by its population problem".

Public-health measures in Mauritius, as elsewhere, are saving infant lives and reducing general mortality. An island community can achieve eradication of malaria and this has been done in Mauritius, where also the infant-mortality rate has been halved in five years, a reduction which took Great Britain nearly six times as long. Moreover, although not specifically mentioned in Mauritius, measures are in hand in developing countries everywhere for preventing diseases such as tuberculosis, whooping-cough, diphtheria, tetanus (triple vaccine), and poliomyelitis; and, most recently, a measles vaccine on a commercial scale is in sight. New drugs for leprosy and trypanosomiasis are being tested and used on an increasing scale in countries where these diseases still cause death and much ill health. The age structure of

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36. Social Policies and Population Growth in Mauritius. By RICHARD M. TITMUSS and BRIAN ABEL-SMITH, assisted by TONY LYNES. London: Methuen. 1961. Pp. 308. 15*s*.

Mauritius is already changing. Soon half the population will be dependants under 15 years of age (the comparable figure in north-west and central Europe is only a quarter); and to make things worse, the island's economy depends essentially on one crop—sugar. Fluctuating world prices and seasonal work bring the paradox of unemployment and difficulties in securing adequate labour by the sugar companies. Better health may increase the productivity of the male workers, but this is little help unless there is work for them all the year round.

Professor MEADE gives helpful advice on the future economic structure of the island, including a very important plea for the maintenance of the quality of leading administrators and the need for additional payments by the United Kingdom for expatriate officials as " one of the most valuable forms of technical assistance which the United Kingdom can render to Mauritius at the present time ". For Professor TITMUSS, the essential solution lies in family planning, which he strongly urges despite the fact that nearly half the population of Mauritius is Roman Catholic. He has detailed and valuable proposals on social-security benefits, but pleads that unless these are accompanied by a family-planning service he would prefer to see his report rejected. The " three-child family " is the basis of the proposals, with an insistence on later marriage and financial support for families who space their children, and no additional benefits for dependent children in excess of three. The fundamental problems of medical care and the proposals for an improved and expanded health service are summarised elsewhere in this issue (p. 551). Smaller families and healthier people, backed by Professor MEADE's far-reaching suggestions for economic expansion and stability, offer Mauritius relief from a grim future.

The lessons of these two reports should be widely studied in other territories for which Britain has an existing or some continuing responsibility. The Gambia is virtually an island surrounded by foreign territory and is dependent on the single crop of ground-nuts. Sierra Leone may see its diamond production exhausted and iron ore worked out. Ghana and Nigeria face the same sequel to improvement in child health—an increase in population at the non-productive age. All these territories are short of medical care and high-quality administration. In Mauritius not only are more doctors needed but there must also be a raising of ethical standards and more control over pharmaceutical products. Preventive measures do not necessarily mean a fitter and healthier population. But always in the background is the fact that " the more successful medicine is in controlling the death rate the greater the problem becomes of controlling the birth rate ". MALTHUS was concerned with the agricultural aspects of population changes and these are fully discussed in Professor MEADE's report. What was not foreseen was the interference by modern medical science in the natural control of population. Yet the medical profession cannot go into reverse. The dilemma of the present and future in Mauritius and elsewhere lies just here. Family planning seems the only answer. Will the community accept this or blindly prefer destruction as deadly as the cyclones, though more prolonged and less spectacular?

Annotations

TOMORROW'S COURTS

ONE of the defects of our penal system is that treatment, as practised at its best by the prison and probation services, is far in advance of diagnosis, as practised by the criminal courts. The report of the Interdepartmental Committee on the Business of the Criminal Courts,[1] a small but admirably selected body, is therefore opportune. The first official systematic survey of its kind, it is a valuable addition to the present flow of reformatory documents.

In essence the committee, in official language, challenge the obstructive " eye-for-an-eye " formula that demands the automatic infliction of punishment by " tariff " according to the nature of the crime, without regard to the nature of the criminal. They point out that " in a considerable, and growing, number of cases the ' tariff system ' can no longer be relied on to fit all the considerations in the court's mind. The need to deter or reform the offender, the need to protect society and the need to deter potential offenders may in a particular case be conflicting considerations." They press for more information at every stage—before, during, and after trial —to help the court towards the sentence that offers the best hope of reform, even when this may mean delaying sentence after conviction. These extra tasks will throw a great deal of work on the probation service, which is already carrying a heavy burden.

The committee are also anxious to educate the " sentencer". They suggest that he should receive a comprehensive account of what each form of sentence entails, what it was designed to achieve, what in fact it has achieved, and the results of the latest research. He would be expected to visit penal institutions. Besides being given detailed information about the circumstances and life of each offender, he would receive periodic reports on the progress of each under treatment and of further convictions.

These proposals, in particular the last (which was lately discussed in these columns[2]), seem to suggest that the " medical " view of crime is spreading.

Much of the report is concerned with proposals to speed the whole judicial process. Eight weeks is suggested as the maximum time any case should wait between committal and trial. Time in custody should be deducted from the eventual sentence (if any). To bring this about the committee want, among other things, a wider range of offences to be dealt with by " summary jurisdiction ". This proposal would save money, which might help to meet the extra cost of some of their other suggested changes. They would like to make quarter sessions a " legally continuous court " able to sit as often as

1. Report of the Interdepartmental Committee on the Business of the Criminal Courts. Cmnd. 1289. M.H. Stationery Office, 1961. Pp. 143. 7s. The members were Mr. Justice Streatfeild, M.C. (chairman), Mr. J. Roland Adams, Q.C., Mr. T. H. Evans, C.B.E., Dr. T. C. N. Gibbens, Mr. J. G. Harries, Sir David Hughes Parry, Q.C., Prof. W. J. H. Sprott, Baroness Wootton of Abinger, and Miss Nora Wynn, O.B.E., J.P.
2. *Lancet*, 1960, ii, 1177.

necessary, to extend the assize circuits, and to appoint four extra judges of the High Court.

So far as they go, these proposed changes are on the right lines and should be introduced without delay. But the committee were only asked to report on arrangements for bringing criminals to trial and for providing the courts with information. As they note rather sadly, their terms of reference did not cover " the basic procedures for determining the soundness of the charges made against an accused person ", but they do record that many hold the present procedure to be outmoded. Perhaps this report will stimulate the Home Secretary to arrange for the critical re-examination of the court as a fact-finding instrument which Dr. Richard Fox lately proposed.[3] If the examination could be made by a committee like this one, it would be thorough and penetrating.

LIVER CANCER AND CIRRHOSIS IN AFRICA

Prof. Paul Steiner embarked in 1957 on a study of liver cancer, cirrhosis, and related diseases in Trans-Saharan Africa and compared the findings with those on similar diseases in the European living in Africa and in the American Caucasoid and Negroid.[4] He hoped to shed light on the ætiology and genesis of liver cancer, and especially to distinguish hereditary from environmental factors. Much had already been written about these diseases in Africa (Steiner cites 78 papers); but a study by one man of all the material was called for, and this task required thousands of miles of travel.

In Africa, postmortem material from 904 cases of liver cancer, 943 cases of cirrhosis, and 1000 cases of parasitic, infective, and nutritional liver diseases was examined and compared with 140 cases of liver cancer and 412 of cirrhosis from Los Angeles and Chicago. In Africa liver cancer is very much commoner than cirrhosis, whereas in America the reverse is the case. Of the 904 cancer patients in Africa, 876 were " natives " from many ethnic groups, 14 were " Cape Coloured ", and 14 " European ". Naturally, not all the information required was available in every case; but great credit is due to the hospital services in Africa, and especially to the pathologists, for the thorough way in which they had collected the material for the survey. Although the incidence of disease cannot be estimated precisely in Africa, it seemed that necropsy records of liver diseases did reflect the incidence in the populations.

The livers of Africans with cancer were large, the average weight being 3390 g., even though Africans are usually of small build and the livers not fatty. Where cirrhosis was present as well as cancer, the livers were usually smaller. The cancers were nearly always (97%) hepatocellular and unicentric, cholangiocellular tumours being more infrequent than in the U.S.A. This was interpreted as indicating that the added cases in Africa were of the hepatocellular type. Davies [5] had previously estimated that in males primary liver carcinoma was about ten times as common in Uganda as in Denmark, where the incidence resembles that in the U.S.A., but that a difference for women had not been shown. Higginson and Oettle [6] found much the same ratio in the Johannesburg area.

The incidence of liver cancer is high among all the major races of Africa, and as each race includes many tribes the idea that this is particularly a Bantu disease cannot be upheld. There was, nonetheless, good evidence that liver cancer is commoner in some groups than in others—for example, in Mozambique than in Transvaal natives and in Ruandi than in Ugandans, and in natives of all kinds than in Europeans. 87% of all the liver cancers were in males, and this preponderance was universal. Steiner was unwilling to accept this at its face value, for males use the hospital facilities more than females. But the disease is common also in European and Cape coloured males and in males in the U.S.A. The average age for the development of liver cancer in Africans was 38 years—about twenty years earlier than in Europeans in Africa or in the U.S.A.

The relation of liver cancer to cirrhosis has been the source of much speculation. Steiner claims that liver cancer is commoner than pure cirrhosis in all parts of Africa, but he includes the 44% of livers with cancer and cirrhosis together among the carcinomas. As 32% of Africans with liver cancer did not have cirrhosis, the latter disease by itself cannot be the sole cause of the cancers. The cirrhosis usually consisted of non-fatty, postnecrotic fibrosis, and the risk of cancer was no greater in severely cirrhotic livers than mildly cirrhotic ones; but the proportion of cirrhotic livers of the severest grade was highest at Dakar and Stanleyville, where the frequency of liver cancer seemed also to be the highest. Non-cancerous livers often were very severely fibrotic, which may mean that the period at risk was less. Nor did the presence of cirrhosis hasten the development of cancer, for the average age of patients with both liver carcinoma and cirrhosis was the same as that of those with cancer alone. Steiner suggests that the cause of both cirrhosis and cancer is the same, resulting sometimes in the one, sometimes in the other, and sometimes in both, with no evidence that cirrhosis itself is a precancerous lesion. Alcohol and dietary liver siderosis (the latter conspicuous only in the Transvaal) are dismissed as causes of liver cancer. Nor does Steiner believe that malnutrition can be a direct cause, since fatty infiltration was not found in the cirrhosis cases, the cirrhosis did not conform to the nutritional type, and the patients with cirrhosis were not undernourished. Moreover, kwashiorkor and liver cancer were not associated, and biopsy showed no sequence from infantile malnutrition to cirrhosis. The lesions of African schistosomiasis were quite different from those of cirrhosis and were not found within the cancers, and in those areas of Africa where malaria was most prevalent the incidence of liver cancer was lower than usual.

Steiner emphasises that in Africa the cirrhotic liver is small, non-fatty, and coarsely nodular, with irregular cell-rich scars, designated postnecrotic. This may result from toxic or infectious causes, but it has not yet been shown to result from malnutrition. The cause is unknown, but Steiner suggests that it may follow viral infections—including Rift Valley fever, Wesselsbron fever, infective hepatitis, or infection with other viruses. Epidemics of infective hepatitis have been reported in Trans-Saharan Africa,[7 8] and the incidence was high among American military personnel in the 1939–45 war in North Africa. Cases of cirrhosis apparently following infective hepatitis were seen in hospitals and at necropsy in most of the areas studied—notably in Lagos and Dakar. As cirrhosis is believed to be an uncommon sequel of infectious jaundice

3. Fox, R., *ibid.* Feb. 18, 1961, p. 392.
4. Steiner, P. E. *Cancer*, 1960, **13**, 1085.
5. Davies, J. N. P. *Acta Un. int. Cancr*, 1957, **13**, 606.
6. Higginson, J., Oettle, A. G. *ibid.* p. 602.
7. Charmot, G., Camain, R., Giudicelli, P. *Bull. Soc. Pat. exot.* 1953, **46**, 847.
8. Hudson, N. P. *Trans. R. Soc. trop. Med. Hyg.* 1931, **24**, 453.

in most countries, some special factor—possibly malnutrition—may account for such a sequence in Africa.

The older opinion that cirrhosis itself predisposes to cancer, based on studies in countries where cirrhosis is far more common than cancer, is weakened by the suggestion from Steiner's study that both diseases may be caused by the same agent—for example, infective hepatitis. The fact that the predominant African cirrhosis is non-fatty and postnecrotic supports the latter view. No unique types of cirrhosis were found in Africa, apart from schistosomal cirrhosis. The cirrhosis with siderosis, thought to originate from the use of iron cooking-pots in the Transvaal, resembles post-transfusion hepatosiderosis.

This authoritative study of liver cancer and cirrhosis in Africa is timely, for changing habits may bring about changes in the incidence of these two diseases, which may eventually give a clue to their ætiology. For the present, infective hepatitis or other virus infections have not been definitely established as causes of cirrhosis or cancer.

EFFICACY OF KILLED POLIOMYELITIS VACCINE

THE protection afforded by killed poliomyelitis vaccine has generally been satisfactory. In England and Wales, Geffen and Spicer have analysed the figures for 1958 and 1959.[1,2] In both years the incidence of poliomyelitis in children under 15 years of age was higher among the unvaccinated than among the vaccinated. Taking all cases together, paralytic and non-paralytic, the rates were 3·4 per 100,000 for vaccinated and 21·1 for unvaccinated in 1958 (those classed as vaccinated had had two or more doses, and those classed as "unvaccinated" one dose or none at all). In 1959 the rates for cases with paralysis (excluding those with one dose from the vaccinated group) were respectively 1·4 and 12·4 per 100,000. Paralytic cases are much likelier to be due to infection with poliovirus than non-paralytic cases, and therefore give a more valid estimate of the effectiveness of vaccination. Lennette et al.[3] have shown that poliovirus can be identified as a cause of paralytic disease more rarely in vaccinated than in unvaccinated cases. The viruses other than poliovirus which can cause paralytic disease have been recently reviewed in these columns.[4]

Although these latest figures show that killed vaccine is fulfilling expectations from the original field trial, substantial numbers of cases occur even in the fully vaccinated. In England and Wales in 1959, of 739 cases of paralytic poliomyelitis 40 were in patients who had had three doses of vaccine. Similarly, in the U.S.A.[5] preliminary analysis shows that last year of 2088 paralytic cases in which the vaccination status was known no fewer than 520 had followed three or more doses of vaccine. In 1958 Israel had an extensive epidemic of poliomyelitis in which the incidence of paralytic disease in vaccinated individuals was alarmingly high. In the age-group 0–5 years the incidence was 17·8 per 10,000 in those with one or no doses, and 45·3 in those with two doses. Davies et al.,[6] in an account of the epidemiology of poliomyelitis in Israel from 1952 to 1959, conclude that the vaccine was 58% effective in preventing poliomyelitis in children aged 6–18 months given two doses of vaccine and severely exposed a year later. It was necessary, in assessing the effectiveness of vaccine, to confine analysis to a narrow age-band because of the rapidity with which natural immunity is acquired in Israel. It was found that 4-year-olds had a rate of poliomyelitis about an eighth of that of 1-year-olds. Hence, it can be said that (in Israel) being 4 years old confers 88% protection against poliomyelitis. It is because the vaccine is not completely effective and because of this age effect that, when all the children under 5 are considered, the attack-rate appears higher in those given two doses. The rate is very much lower (8·4 per 10,000) in children given three doses, because by the time the third dose is given the children are a year older and the protective effect of age is added to the protective effect of vaccine.

The vaccine used in this country elicits very effectively antibodies to types 2 and 3 in almost all children over 1 year old, producing titres of over 1/100 after a booster dose. Of 172 young adults initially without antibodies to any of the three types, inoculation failed to produce levels of 1/100 to types 2 and 3 in 3 and 8 respectively.[7] The results for type 1 are considerably less good, and furthermore they vary from one batch of vaccine to another. Kendall et al. earlier concluded from studies on the rate of decline of antibodies that, in order to maintain immunity for five years, a level of at least 1/100 should be achieved. They now find that after the first eighteen months the subsequent decline of antibodies proceeds more slowly.[8]

Sabin [9] has contended that, with proper leadership, a vigorous campaign of immunisation with attenuated vaccine can rapidly eliminate poliomyelitis in the U.S.A., in a way that may take years or never be possible with killed vaccine. Payne [10] believes that attenuated vaccines, at least those incorporating Sabin's strains, have now been proved safe. He holds that the serological evidence of the efficacy of this form of vaccine is virtually conclusive; but he reiterates that more than one feeding is required for uniform success, and looks forward to a slower introduction of attenuated vaccine than Sabin. Smorodintsev et al.[11] have reported experiences with attenuated vaccine in Russia. Apparently the vaccine has proved safe and effective in preventing poliomyelitis, though, because of the lack of an adequately controlled trial, this conclusion is not absolutely certain. They obtained the best results by giving first type 1, then types 2 and 3, and, finally, all three types together.

The W.H.O. expert committee on poliomyelitis [12] has, for the present, not recommended the use of attenuated vaccine in parts of the world where there are significant numbers of non-immune adults; for it fears that such adults, being more vulnerable to poliovirus than children, may acquire infection from contacts with children given vaccine. For developing areas, many of which have a high incidence of poliomyelitis,[13] an attenuated vaccine has many attractions [10]; but in this country it is probably best to persevere with killed vaccine, which can now be made

1. Geffen, T. J., Spicer, C. C. *Lancet*, 1960, ii, 87.
2. Geffen, T. J. *Mon. Bull. Minist. Hlth Lab. Serv.* 1960, **19**, 196.
3. Lennette, E. H., Magoffin, R. L., Schmidt, N. J., Hollister, A. C. *J. Amer. med. Ass.* 1959, **171**, 1456.
4. *Lancet*, 1960, ii, 1184.
5. Poliomyelitis Surveillance Reports, U.S. Communicable Diseases Center, no. 220, Jan. 13, 1961.
6. Davies, A. M., Marberg, K., Goldblum, N., Levine, S., Yekutiel, P. *Bull. Wld Hlth Org.* 1960, **23**, 53.
7. Kendall, E. J. C., Vollum, R. L., Beswick, T. S. C., Miller, A., Tobin, J. O'H. *J. Hyg., Camb.* 1960, **58**, 399.
8. Kendall, E. J. C., Miller, A., Tobin, J. O'H. *Brit. med. J.* Jan. 21, 1961, p. 176.
9. Sabin, A. B. *Arch. intern. Med.* 1960, **106**, 5.
10. Payne, A. M.-M. *Bull. Wld Hlth Org.* 1960, **23**, 695.
11. Smorodintsev, A. A., Drobyshevskaya, A. I., Bulychev, N. P., Chalkina, O. M., Groisman, G. M., Ilyenko, V. I., Kantorovich, R. A., Kurnosova, L. M., Vasilyev, K. G., Votyakov, V. I., Zhilova, G. P. *ibid.* p. 705.
12. Expert Committee on Poliomyelitis: Third Report. W.H.O. *Tech. Rep. Ser. Wld Hlth Org.* 1960, no. 203.
13. Akers, T. G., Hashem, N., Mahdy, M. S. *Amer. J. trop. Med. Hyg.* 1960, **9**, 343.

satisfactorily potent.[14 15] With the present vaccines a fourth dose should be given to ensure continued protection; but Salk [16] has suggested that it may be possible to produce a vaccine of which only a single dose will be needed. Quadruple vaccine, including poliomyelitis vaccine, is likely to prove satisfactory [17] and has substantial administrative advantages. Attenuated poliomyelitis vaccine still poses some difficult problems—not least that of immunising most members of a community in a few days, which seems to be a requirement for success. The discovery of vacuolating virus [18] in many seed lots of the vaccine raises doubts about its long-term safety. Exclusion of known contaminating viruses from the vaccine is extremely difficult, and there is an ever-present fear that unknown viruses may be incorporated. What little we know about tumour viruses [19] suggests that it is unwise to use a possibly virus-contaminated living vaccine when there is an inactivated alternative.

UNEASY SOCIETY

THE Bristol Social Project, in its first short report,[20] has some challenging things to say about contemporary social organisation. The Project, which occupied eleven workers for varying periods between 1953 and 1958, was designed to discover how small urban communities, such as those on new housing-estates, can be helped, mainly by group-work techniques, to cope with their own social problems.

While nothing very new emerges, the findings will be valuable in focusing attention on some of the causes of maladjustment in modern industrial society. Specialisation of employment and a comparatively high degree of social and geographical mobility have characterised post-war Britain, and as a result of rehousing and slum-clearance schemes a great many people have been exposed to entirely new kinds of stress and strain. Individual reactions to new environments vary enormously, but there is good reason to believe that some people react by antisocial behaviour while others take refuge in depression and illness. One of the most interesting findings is that on a new housing-estate the general practitioner is largely occupied in providing emotional support; many people visit their doctors for reassurance.

The report brings out very clearly the sense of loneliness which particularly afflicts those mothers who can no longer rely on the traditional forms of help from kinsfolk. Such people are prey to the "suburban neurosis" described by Taylor [21] in 1938. Merely discovering the possibility of friendship and the knowledge that others were in the same plight seemed to have a reassuring effect on many disturbed housewives. But perhaps the most striking part of the report concerns the activities of teenagers—especially those of an aggressive and delinquent group of boys and girls who were only on the fringe of the orthodox club movement. The relationship which the unattached group worker was able to build up with one mixed gang, and their subsequent history as an informal quasi-club, reveal the acute tension that exists between social workers and members of the general public on the topic of law and order. This misunderstanding between the professional worker and the layman is crucial to any future attempt to bring aggressive, suspicious, and anti-social young people more into line with the general culture.

The group worker was commonly accused of siding with the delinquents, of failing to keep them under control, and of stimulating their wild behaviour. Most decent citizens wrongly imagine that the controls which are effective with their own socialised children and which were efficacious in their own early days are appropriate for these hostile and dissocial youngsters who cause most of the trouble. What to the normal boy and girl is discipline is to the disaffected youth but one further indication that society is against him. The only hope of reconciliation is for social workers, as representatives of the wider society, to try to convince these rebels that they are, despite their delinquencies, loved and valued citizens. And if this slow and difficult task is to be performed by social group workers on our behalf, then the whole adult community must decide to support them. The present ambivalence with regard to teenage deviants will achieve nothing but further frustration. Those whose business it is to formulate social policy and those who carry out the field operations must have the full confidence and sympathy of us all if they are to succeed. The alternative is continuing hostility between the generations with all that this means in terms of individual unhappiness and public unease.

THEORY OF VISION

FOR an Edridge Green lecture delivered last year at the Royal College of Surgeons and now published,[1] Weale chose as his topic the Duplicity Theory of Vision. This title at once makes us at home, for we remember that rods are used for twilight and cones for daytime, and at first the lecture looks like a comfortable exposition of views old enough to be respectable and unlikely to provoke us to the irritation of new thought. But the happy simplicity of the rod *v.* cone view is not allowed to rest long in peace. Do rods and cones play Box and Cox, or can both act together? Are they independent or organised in a web of neural facilitation and inhibition? How are thresholds related to the quantity of visual pigment and how to the size of receptor clusters? How again do these two features change in light and dark adaptation? These are important questions; and, though they have often been asked in the past twenty years, Weale is right to put them again.

He brings forward experimental evidence both from the work of others and from the results which he and his colleagues have obtained at the Institute of Ophthalmology. He showed (with G. B. Arden) that visual thresholds obtained during dark adaptation improve in a way which depends on the size of test flash employed. This confirms the earlier work of Craik and Vernon,[2] and is incompatible with the view that thresholds depend only on the regeneration of visual purple. Weale's most recent work is in the very difficult technique of measuring visual pigments objectively by reflection from the human eye. Such measurements were discussed by Rushton [3] in the previous Edridge Green lecture, and it is satisfactory to note that these two investigators agree substantially.

14. Hilleman, M. R. Paper presented at the 5th International Poliomyelitis Conference, Copenhagen, 1960.
15. Perkins, F. T. Paper read at Symposium on Stimulation of Antibody Production, British Society for Immunology, No. 25, 1960.
16. Salk, J. E. *Lancet*, 1960, ii, 715.
17. *ibid.* p. 1385.
18. Sweet, B. H., Hilleman, M. R. *Proc. Soc. exp. Biol., N.Y.* 1960, **105**, 420.
19. McCulloch, E. A. *Canad. med. Ass. J.* 1960, **83**, 1049.
20. Relieving Stresses of Living on Council Estates. Bristol Social Project, the Council House, Bristol.
21. Taylor, S. *Lancet*, 1938, i, 759.

1. Weale, R. A. *Ann. R. Coll. Surg. Engl.* 1961, **28**, 16.
2. Craik, K. J. W. Vernon, M. D. *Brit. J. Psychol.* 1941, **32**, 62.
3. Rushton, W. A. H. *Ann. R. Coll. Surg. Engl.* 1959, **25**, 79.

ANTINUCLEAR FACTOR

THE serum of patients with systemic lupus erythematosus contains antinuclear factor (A.N.F.), which comprises one or more γ-globulin components that bind with antibody-like specificity to somatic cell nuclei. This property of the serum is demonstrable in vitro by tests usually involving the use of fluorescein-labelled antibody against human globulin to reveal (by ultraviolet microscopy) uptake of the specific factor from the patient's serum by nuclei of fresh leucocyte smears [1] or frozen unfixed tissue sections,[2] or by nucleoprotein spots dried on to slides.[3]

Most workers agree that this serum factor is present in almost every case of systemic lupus, but it is uncertain whether this factor is always associated with the lupus serum factor which sensitises and alters leucocyte nuclei in the L.E.-cell test. One reason for this uncertainty is that A.N.F. seems to be distributed more widely in disease than the positive L.E.-cell test. Apart from systemic lupus, positive L.E.-cell tests are not common, although they have been reported in rheumatoid arthritis, in other connective-tissue conditions, and in liver disease. A.N.F. is identifiable in all these conditions with significantly greater frequency, although never as consistently as in systemic lupus. The facts that it reacts with nuclei, and even binds to the patient's own cell nuclei, suggested that it might be an autoimmune feature, similar to the autoantibodies directed against other cellular constituents which are so commonly found in systemic lupus.

Holborow [4] has found A.N.F. in the sera of about 10% of cases of autoimmune thyroiditis, and Friou,[5] Holborow and Weir,[6] and Duthie et al.[7] have found positive tests in 10–50% of cases of rheumatoid arthritis. Such wide variation may be due partly to case selection, and partly to differing sensitivities of methods for the demonstration of A.N.F. Alexander et al.,[8] in an extensive survey by means of the fluorescent-antibody method with leucocytes of human blood films as substrate, found A.N.F. regularly and in highest titre in sera from cases of systemic lupus; but in 183 cases of rheumatoid arthritis they report positive results in as many as 65% (the majority in the more active cases) but with a rather lower average titre than in lupus. They also found a surprisingly high proportion of positives in osteoarthritis (22%) and in "other rheumatic" conditions, and 17% of miscellaneous hospital cases gave positive tests. They report an appreciable proportion (4%) of positives in the healthy; and this seems to indicate that the test used was especially sensitive, since previous workers have seldom found normal sera positive. Hall et al.,[9] who used human skin sections as substrate, report that 36% of 130 patients with rheumatoid arthritis had directly demonstrable A.N.F. in their sera, but that normal sera (with 1 exception) were negative. In this study, 14% of miscellaneous hospital cases gave positive A.N.F. tests, and in more than half these positives the patients had had musculoskeletal disorders. In both these surveys scleroderma, dermatomyositis, and polyarteritis yielded positives. It is only to be expected that a complex fluorescence method involving different substrates should yield results which vary considerably in different hands. Pollak et al.[10] have also obtained positives in sera from healthy subjects. These workers used buccal mucosal smears as a source of nuclear material, and found that most normal sera became negative at 1 in 4 dilution; in contrast, among 50 relatives of 12 patients with lupus erythematosus they found 24 positive at 1 in 4 dilution and upwards—which suggests that in this disorder, at any rate, there may be a familial aspect to A.N.F. production.

In summary, then, the present position is this. In systemic lupus erythematosus even relatively crude fluorescence methods will reveal A.N.F. (usually in high titre) in practically all cases. Sensitive methods, on the other hand, will reveal a few (usually low-titre) positives in the apparently healthy. Positives are found in some cases of rheumatoid arthritis—with sensitive methods in about 50%. A.N.F. may also be found in other connective-tissue disease, in discoid lupus,[4] and in liver [11] and thyroid disease. The fluorescent-antibody test detects A.N.F. in all these conditions simply as globulin taken up by nuclei. Goodman et al.,[12] however, have shown that in lupus serum antinuclear activity can reside in both 7S γ-globulin of "normal" molecular weight and in the heavy 19S macroglobulin, and that both fractions can give positive fluorescence tests. Hall et al. found that some rheumatoid sera negative on direct testing yielded a euglobulin fraction which gave a positive reaction; this too may involve a macroglobulin, whose production may possibly be linked to that of rheumatoid factor—another macroglobulin with immunological activity. The significance of A.N.F. in these conditions, like that of rheumatoid factor in rheumatoid arthritis, is obscure; but it seems unlikely to be of direct ætiological importance. Clinicians find this a useful test, since a diagnosis of systemic lupus is unlikely if the test is negative. In research, detection of A.N.F. plays a part in helping to map the distribution of disease-groups in which antibody production is disturbed.

NEW JOURNAL OF MYCOLOGY

THE first issue of *Sabouraudia*,[13] the journal of the International Society for Human and Animal Mycology, indicates some of the scope of recent advances in this subject. While classification and taxonomy should be left largely to the trained laboratory worker, the practising doctor and veterinarian may still select material and also contribute ideas that lead to new lines of investigation. This is illustrated by the first four papers on clinical and experimental work. All four are about candida, a fungus which readily changes from saprophyte to parasite. This theme of the saprophyte-parasite relationship recurs again and again, and there are two interesting papers on the "perfect" state of some well-known dermatophytes—the first by Phyllis Stockdale on *Microsporum gypseum*, and the second by Christine Dawson and J. C. Gentles on *Keratinomyces ajelloi*, *Trichophyton terrestre*, and *M. nanum*. Knowing that these fungi could live in keratin, and using Vanbreuseghem's technique, Stockdale, Dawson, and Gentles grew them in soil baited with hair, and succeeded in producing cleistothecia—"perfect" sexual forms. The results may call for some revision of the

1. Holman, H. R., Kunkel, H. G. *Science*, 1957, **126**, 162.
2. Holborow, E. J., Weir, D. M., Johnson, G. D. *Brit. med. J.* 1957, ii, 732.
3. Friou, G. *J. clin. Invest.* 1957, **36**, 890.
4. Holborow, E. J. *Proc. R. Soc. Med.* 1960, **53**, 625.
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classification of the dermatophytes. The last paper, by D. W. R. Mackenzie, describes an ingenious method he devised for detecting *T. tonsurans* infection in girls in a residential school by examining cultures taken from hair-brushes, pillowslips, and other articles, the evidence of infection in some of their scalps being so slight that it might otherwise have escaped detection.

The journal is edited by Dr. J. C. Gentles, who has set a high standard.

RENAL-ARTERY OBSTRUCTION

IN a small proportion of cases of persistent hypertension, the disorder arises neither from bilateral renal disease nor "idiopathically", but from one of a group of relatively rare disorders, such as hyperaldosteronism, phæochromocytoma, and unilateral renal disease, which do not always manifest themselves by characteristic symptoms or signs. It is particularly important to diagnose these disorders because often they can be treated effectively. Yet in each the diagnostic procedures are time-consuming, costly, and available only in special centres, so their application to all patients with persistent hypertension is impracticable. It is encouraging to learn of the simplification [1] of a diagnostic procedure for one of these conditions—renal-artery obstruction.

Some ten years ago three groups [2–4] showed that, in dogs in which both ureters were catheterised, gradual narrowing of one renal artery produced a fall in the volume and sodium concentration of the urine from the ischæmic kidney compared with that from the control kidney. In 1954 Howard et al.[5] reported a similar diminution of urinary volume and sodium concentration on the affected side in a patient in whom aortography had revealed constriction of one renal artery. Three years later [6] it was shown that this observation could be used to pick out patients with unilateral partial renal arterial obstruction from those whose hypertension was "essential" or was caused by bilateral renal disease. The test is positive only if both the volume and the sodium concentration of the urine are reduced. Thus in a group of patients in whom intravenous pyelography and arteriography had revealed a unilateral renal lesion with some narrowing of the renal artery, but in whom nephrectomy had not produced a fall of blood-pressure, the urinary volume from the affected side was smaller than that from the normal side but the sodium concentration was equal or greater. Nephrectomy produced a sustained lowering of the blood-pressure only when the urine from the affected kidney had both a smaller volume and a lowered sodium concentration. The test thus seems to identify cases in which the unilateral renal lesion is contributing, presumably via the Goldblatt mechanism, to the hypertension and in which nephrectomy or plastic arterial surgery will be effective.

One technical difficulty invalidating many such tests is the leakage of urine around the ureteric catheters. Rapoport [1] now reports that on the affected side the creatinine concentration of the urine is higher than on the normal side. Thus the urine-to-plasma ratio of creatinine is higher, and that of sodium lower, on the affected side; and the difference between the two sides can be emphasised by dividing the one ratio by the other. The tubular-rejection-fraction ratio (T.R.F.R.) thus obtained is expressed as

$$\text{T.R.F.R.} = \frac{\text{Urinary sodium conc. (lt.)}}{\text{Urinary creatinine conc. (lt.)}} \times \frac{\text{Urinary creatinine (rt.)}}{\text{Urinary sodium conc. (rt.)}}$$

and its calculation does not involve estimations of plasma concentration nor an accurate knowledge of the urinary volumes. The range for the T.R.F.R. in patients with hypertension arising from causes other than unilateral partial renal artery obstruction is 0·62–1·62. With obstruction on the left side the T.R.F.R. is below the lower limit, with obstruction on the right side the T.R.F.R. is above the upper limit. Cases of unilateral pyelonephritis fall within the normal range. The T.R.F.R. does not reveal obstruction to a branch of the renal artery even if this is causing hypertension, nor does it reveal bilateral and equal occlusion. False positive values may arise if ureteral catheterisation relieves an obstructed ureter; for then sodium diuresis may ensue, and the opposite side be wrongly incriminated.

The data recently published by Peart and his colleagues from St. Mary's Hospital [7] enable the T.R.F.R. to be calculated and largely confirm its diagnostic usefulness. Their results indicate, too, that the ratio will not reveal stenosis of a branch of the renal artery.

Almost all hospitals will have the necessary surgical and biochemical facilities to determine the T.R.F.R., but the difficulty of deciding which hypertensive patients should be investigated remains. Rapoport's results indicate quite clearly that the T.R.F.R. may be positive when the intravenous pyelogram is normal. Peart and his colleagues [7] remark that many workers have not appreciated that the dye is usually concentrated abnormally well on the affected side, and this observation may be important diagnostically. Aortography, because of its hazards, should be undertaken only when the T.R.F.R. is abnormal. Renal-artery disease is responsible for 5–10% of all cases of severe hypertension, and it may be necessary to determine the T.R.F.R. in every case where the cause is obscure. Certainly, when hyperaldosteronism is suspected, renal-artery obstruction must be carefully excluded, in view of the recent observation [8] that excretion of aldosterone is commonly increased in cases of unilateral occlusion.

Lord STOPFORD of Fallowfield, F.R.S., formerly vice-chancellor and professor of experimental neurology in the University of Manchester, died at his home in Westmorland on March 6. He was 72 years of age.

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INDEX TO THE LANCET

FORMERLY the index was sent only to those who asked for it, but now it goes to all subscribers. The index and title-page to vol. II, 1960, which was completed with the issue of Dec. 31, is enclosed with each copy of our present issue.

As we may not be able to supply indexes to binders, orders for binding the collected issues are best deferred until the index can be sent with them.

Public Health

LOCAL-GOVERNMENT REFORM IN LONDON

Last October a Royal Commission made revolutionary proposals for the future government of London.[1] It suggested that the primary unit of local government should be the " Greater London Borough ", having (save for the City) a population of between 100,000 and 250,000. There would be about 52 such boroughs, and they would among other things be fully responsible for the whole range of personal health, welfare, and children's care services, and undertake the day-to-day management of schools, including the school health services. For the whole area, a Council for Greater London, elected triennially, would be the education and planning authority, and the authority for traffic, main roads, refuse disposal, and the fire and ambulance services.

VIEWS OF THE L.C.C.

Invited to comment on the Royal Commission's plans, the London County Council last week approved a highly critical report by their general purposes committee. This says that the proposals—involving disappearance of the counties of London and Middlesex, truncation of Essex, Kent, and Surrey, reduction in the size of Hertfordshire, reduction in the status of three county boroughs, and reorganisation of some seventy authorities of the second tier—would mean reorganisation of unprecedented complexity: " almost every service which had hitherto been organised as a whole by one authority would be dismembered, divided, and distributed ". The period of transition would be very difficult, and the difficulties would fall on local-government staff of whom there was a shortage. The upheaval could be justified only by assurance of compensating improvement, but there was no such assurance.

The Royal Commission was concerned alike with administrative efficiency and with the health of representative government; and it concluded that the town hall is the proper focal point for local administration, and that areas larger than boroughs of 100,000–250,000 are likely to create too remote an administration. The L.C.C., however, hold that the commissions attach too little importance to efficiency. The council agree that an important element in municipal services —especially in " personal " services such as health, welfare, and the care of children—is that they should not be impersonal; but the commission " does not appear to have had before it any evidence to show that any service provided by the Council was more remote or less personal than it might have been ", and assertions that those to be provided by the Greater London boroughs would be more sensitive are statements of faith not of fact. Much depends on the local-government officer, and the L.C.C. doubt whether some of the smaller authorities will be able to recruit an adequate staff.

In some cases, they point out, a Greater London borough might inherit the facilities it required for an efficient service, but in many cases it certainly would not. Moreover the new boroughs would in no sense represent social communities, but " have been suggested according to an artificial and arbitrary criterion of size which in itself has no special merit, other than the suppositions that the town hall may be ' nearer ' to the citizen than the county hall, and that democratic local government can flourish better in a smaller than in a larger unit". Arguing that an authority with a large area can help towards equality of service throughout that area, the L.C.C. say that " citizens in different parts of the county expect to receive . . . a common standard of public service ", and the cost of this is spread over the county. " Certain local health services are appropriate for devolution upon authorities of the second tier, namely, maternity and child welfare, day nurseries, home nursing and chiropody. These the Council is disposed to confer on the Metropolitan Borough Councils. But there are certain matters which it would be inappropriate or less economical for the second-tier authorities to provide. Examples are, the mental health and domiciliary midwifery service."

The L.C.C. believe that the Council for Greater London, if it came into existence, would have to exercise greater powers than those envisaged. The commission's insistence on the Greater London borough as the primary unit would in fact have the paradoxical result that " the Council for Greater London would become an authority greater than any yet seriously conceived, with full entitlement to all the terms of opprobrium, such as ' monolithic ', ' remote ', ' impersonal ', and (very probably) ' bureaucratic ' which have been applied to the larger type of organisation". In these circumstances local government in Greater London would become regional government—" the very result which the Commission seemed anxious to avoid".

In outlining " an alternative scheme ", the L.C.C. express again their intention and willingness to discuss with the Metropolitan borough councils " the delegation or transfer of further county functions ". Also they agree that certain aspects of local administration might advantageously be considered from the point of view of Greater London as a whole. But these do not call for the establishment of such a body as the Council for Greater London, nor for the abolition of the London County Council.

VIEWS OF THE LOCAL MEDICAL COMMITTEE

Representing some 2200 general practitioners working for the National Health Service, the Local Medical Committee for the County of London has issued its comments on the Royal Commission's report.

" What do we stand to gain? " it asks. Instead of being administered by the L.C.C., which in the commission's own words has provided a " strong and able form of government which makes its standing very high among the municipal governments of the world ", the personal services are to be handed back to Metropolitan boroughs. In experience of the borough councils both before and since 1948, the committee " found widely differing methods and standards, and only rarely any willingness to cooperate ". Though there are striking individual exceptions, " the average quality of both members and officers is lower than it is on the County Council, and the degree of statesmanship and cooperation much less".

With the commission's contention that purely local decisions should be taken by local people, the Local Medical Committee is in complete agreement; though " this can be achieved by other methods than their proposed fragmentation ". But the idea that every citizen should be near enough to the town hall to go there if he has a grievance to ventilate is archaic—ignoring not only the fact that most citizens are fully occupied during the hours when the town hall is open but also the existence of the telephone and letter post. The commission have planned for the Londoner a collection of boroughs where everyone can take part in local politics; but, though this may have been appropriate for a Greek city State in 500 B.C., it is not therefore suitable for a 20th-century London. What the Londoner really wants is good administrative government, and by and large, so far as County Hall is concerned, he is satisfied that he has got it.

Holding that there should be the least possible upheaval of the present structure, the Local Medical Committee suggests that Greater London should be divided into a small number of counties, of which the central one would roughly correspond to the present area of the L.C.C. Each county council would determine policy for the whole of its area, but would decentralise local administration as far as possible, with divisional committees on the lines of the

1. Royal Commission on Local Government in Greater London. Cmnd. 1164. H.M. Stationery Office. 1960. See *Lancet*, 1960, ii, 963.

L.C.C.'s. (Here the Local Medical Committee remarks that it is by no means wedded to the present structure of the L.C.C.'s divisional committees, nor to the number of divisions or their precise powers.)

The City of London should retain its present powers and position. As regards the Metropolitan borough councils, "if we are forced to choose—as it appears we are now forced—between the government of the borough councils and the better government of the County Council, then emphatically we choose the better". It accepts, with reservations, the proposal for a Council for Greater London, "with those local authority functions . . . which can only be effectively performed over the wider area of Greater London or which could be better performed over that wider area".

VIEWS OF THE EXECUTIVE COUNCIL

THE London Executive Council points out that in the National Health Service the areas of executive councils and local health authorities are coterminous. In London, if a doctor needs to get in touch with "the organisation", he contacts county hall or one of the nine divisional offices of the public-health department of the L.C.C. This system works very satisfactorily and London doctors would be very sorry to see it disturbed. They know that the same policy in local health matters, the same arrangements and procedures and the same forms will apply over the whole area. If the local health services were fragmented over a number of boroughs it would immensely complicate the work of the family doctor."

Infectious Diseases in England and Wales

Disease	Week ended February			
	4	11	18	25*
Diphtheria	3	6	16	6
Dysentery	562	705	771	539
Encephalitis:				
Infective	4	3	4	2
Postinfectious	2	8	6	8
Food-poisoning	100	89	81	101
Measles, including rubella	19,213	27,917	30,917	34,863
Meningococcal infection	29	24	29	39
Ophthalmia neonatorum	24	21	14	15
Paratyphoid fever	1	8	3	1
Pneumonia, primary or influenzal	1644	1810	1532	938
Poliomyelitis:				
Paralytic	4	2	2	1
Non-paralytic	..	2	1	1
Puerperal pyrexia	157	214	161	175
Scarlet fever	586	558	610	480
Smallpox	..	..	..	..
Tuberculosis:				
Respiratory	393	409	394	414
Meninges and C.N.S.	6	4	2	7
Other	46	36	55	71
Typhoid fever	2	..	..	2
Whooping-cough	933	748	697	753

*Not including late returns.

The Wider World

WITH W.H.O. IN THE CONGO

JOHN MCFIE
M.D. Cantab.

THE Congo is good in parts. It is not all steamy impenetrable jungle stretching between sluggish crocodile-infested rivers, nor is it all in a state of civil unrest. It is true, I have met a Red Cross surgeon who was arrested while bathing and spent the best part of 24 hours in his bathing shorts, being driven from place to place; and a World Health Organisation doctor who intervened to prevent a summary execution, travelled for some days with the prisoner and his guards in search of a senior officer to whom to appeal—and acted as chef to the party, since he was the only one who could cook! But those were, let us hope, the bad old days: now order, if not law, prevails in some provinces, and United Nations personnel can go about their duties unmolested.

Of all the U.N. agencies, W.H.O. has perhaps the most enviable task in the Congo: its work involves the least association with politics, and the greatest direct assistance to the people. In Luluabourg, for instance, where I have been for the last couple of months, the team includes waterworks and sanitary engineers (Haitian and French), an M.O.H. and public-health assistant (French), three hospital doctors (English, Colombian, and Italian), and a radiographer (Swiss), all under the direction of the provincial medical officer (Israeli) who is also adviser to the provincial ministry of health. When the first members of the team arrived, there were no Belgians in any of these positions. Hanging up in my office is an old list of doctors' telephone numbers; there are 15 names on the list, but they were among the first Belgians to leave. Three nurses refused to go, and for some weeks they, and the nuns who run the maternity ward, carried on in a 500-bed hospital without medical staff.

Administratively, the running of the hospital is no longer in European hands—and therefore not in the hands of doctors. Directors of the hospital and of the departments are young Congolese, formerly *infirmiers* or medical assistants. We Europeans are employed as technicians, and our task in the hospitals is treatment: disciplinary and other matters are referred to the directors. For some of the Belgians, this has been a difficult adjustment to make: "*avant* . . . ", with a shrug of the shoulders, expresses their nostalgia for the past and their disillusionment with the present. So one finds oneself from time to time attempting to calm ruffled tempers; but the directors I have met have been intelligent, aware of their deficiencies of knowledge, and anxious to keep their departments running as well as possible. In times of crisis, however, —as in the recent conflict between the military and civilian populations—they are just as panicky as the other Congolese, and lead the flight of staff from the hospital. On such days, I find myself mixing milk powder, washing babies, and sweeping the floor.

* * *

The hospitals are large, well built, and well equipped—in some cases too well equipped. The Red Cross surgeon told me that while there was a variety of specialised stitching devices, there were no ordinary curved needles; and so much of the equipment is electrical that when the electricity supply fails, the hospital almost comes to a standstill. Repairs and replacements are of course almost impossible to obtain; so the amount of equipment available is slowly dwindling.

Laboratory and X-ray services are sketchy. In the first, a new (Belgian) technician has just arrived, and has not yet had time to make her influence felt: experience has taught me that bacteriology is more reliably done than hæmatology, but they are beginning to run out of chemicals. The larger of the two X-ray machines is out of action, so that only the smallest chests can be taken. A blood-bank exists: it consists only of group-O blood, and no cross-matching is done. Since the donors are all military (who are paid for their contributions) the supply of blood ceases

when there are disturbances. The supply of drugs was copious, and of a wide range, including varieties of corticosteroids and tetracyclines (though still relying for antimalarial therapy, as do many British Colonies, on quinine); but as no-one seems to know who controls the provincial pharmaceutical store nor what it contains, as the budget for 1961 has not yet been drawn up, still less approved, the local supplies of drugs are beginning to dwindle and only emergency action by the W.H.O. adviser secures occasional advances from the central depot in Léopoldville.

Since nearly half of the population is under 15 years of age, the admissions to the children's wards (an average of 6 every day, with a mortality of about 10%) provide an important reflection of the state of health of the community. 60% of the patients (mostly under one year of age) are more or less " ordinary " by tropical standards—malaria, respiratory and intestinal infections, with occasional cases of meningitis, tuberculosis, and sickle-cell anæmia. 40% of the admissions, and half the deaths, are cases of malnutrition (almost exclusively kwashiorkor) the majority of whom are 3, 4, or 5 years old. This is at least five times the proportion found in other countries where kwashiorkor is common,[1] and reflects not only the usual stress on starchy foods but also the disruption of life and food-supplies in rural areas—from which 75% of the cases come. In fact, the Lulua in Kasai are suffering, though on a smaller scale, the same privations as are the Baluba in the much-publicised famine area round Bakwanga. Two of my present patients with kwashiorkor have mothers with kwashiorkor also, and infant sibs with marasmus.

Fortunately there is still plenty of milk powder, and the wardmaids are adept at persuading reluctant children to drink more—or ignorant mothers to persuade them to. But most Congolese who have any notions about diet are still more vitamin-conscious than protein-conscious. Treatment evidently tended to be of the " shotgun " type (to which we probably owe our large stocks of antibiotics); and perhaps excusably so when precise diagnosis is so difficult. One unexpected therapeutic preoccupation is with " heart stimulants ". Seldom am I called at night to a child, whatever its condition, without finding that it has been given nikethamide and camphor along with other drugs. My Australian Red Cross predecessor and I have succeeded in dissuading the ward staff from using these stimulants, but I doubt whether the habit will die easily: the stocks of nikethamide are too large!

Besides work at the hospital, we have managed to start one or two child welfare clinics in the suburbs of the town, and the response has been nearly overwhelming. Those attending are drawn largely from the more intelligent, progressive families; but the weights of the children show the same trend as was found by Dr. Welbourn in Uganda[2]: excellent in the first six months, but falling below the European average thereafter—another reflection of the poor state of nutrition.

Then there are occasional emergencies of a more dramatic nature. One afternoon I spent an hour of fascinated apprehension leaning out of the open door of a U.N. helicopter, looking at the jungle and the swamps a few hundred feet below, on the way to an outbreak of *H. influenzæ* meningitis in a small isolated village. Christmas Day I spent in Bakwanga, where there is quite simply an epidemic of kwashiorkor, and where conditions in such hospitals as there are are appalling and pathetic. When one puts one's stethoscope on the chest of a starving child the projection of the ribs makes it impossible to hear the breath-sounds: all one hears is the crying of the other children in the ward.

* * *

So W.H.O. is, at least, trying to stop the gap—the chasm—left by the departure of the Belgians. Whether we should be doing more, trying to improve on what existed " before . . . ", trying to extend health education or increase preventive measures—these are perhaps, with such limited personnel, academic questions; and, with the atmosphere of improvisation and uncertainty that surround much of U.N.'s work in the Congo, may never be answered.

Nevertheless, it is encouraging to feel that one is stopping a part, however small, of the gap; and the friendliness and interest of the Congolese is an added reward. There are rewards too for those who enjoy oddities, in many features of everyday life. With all the airlifts going on, it is almost easier to get a lift in a plane than in a car. The cost of gin (in the PX) is the same as of 3 lb. of potatoes (in the shops—either of them). Journalists come, with a minimum of notice, expect one to do one's utmost to supply them with information or material to photograph, and then go away without a word of thanks or a print of the photos. And there are kilogrammes, driving on the right, and (of course) French. (If, when answering the telephone, one does not identify oneself, the other person is likely to ask " A qui j'ai l'honneur ? " to which I am sometimes tempted to reply " Vous avez l'honneur . . . ") I had been afraid that my limited command of the language would soon leave me with aphasia, but I find to my relief that the Congolese are much more easy to understand than some of the Belgians or French, and they seem to understand me.

1. Gongora, J., McFie, J. *Trans. R. Soc. trop. Med. Hyg.* 1959, **53**, 238.
2. Welbourn, H. F. *J. trop. Pediat.* 1955, **1**, 34.

Special Articles

THE HEALTH OF MAURITIUS

RECOMMENDATIONS for the future of the health services in Mauritius form part of a report [1] on social security by Prof. Richard Titmuss and Dr. Brian Abel-Smith, commissioned by the Government of the island. We publish below a summary of the chapters specially concerned with the health of the island's population. The report, and a companion one on economic and social structure by Prof. J. E. Meade and his team, are discussed in a leading article on an earlier page.

THE PRESENT SITUATION

The island of 720 square miles has a population of 600,000: 29% are of European, African, or mixed origin, and Catholics by religion; 67% are of Indian descent, Hindus or Muslims; and 4% are Chinese, Catholics or Buddhists.

Medical services are at present provided by (1) the Government Medical Service, which evolved from the provision of medical care to paupers in the 19th century under the Poor Law; (2) the medical services provided by sugar estates for their employees as required by the Labour Ordinance; (3) the maternity and child-welfare services provided partly by the Government and partly by a voluntary body (the Maternity and Child Welfare Society); and (4) private practitioners.

The public hospital service includes 8 general hospitals, and the Princess Margaret Orthopædic Centre, the Brown-Séquard

1. Social Policies and Population Growth in Mauritius. By RICHARD M. TITMUSS and BRIAN ABEL-SMITH, assisted by TONY LYNES. London: Methuen. 1961. Pp. 308. 15*s*.

Mental Hospital, and the Leper Hospital. At the end of 1959 there were 2266 beds; and in 1958 the total number of hospital admissions was 34,766—about 15·3 patients per bed (England and Wales, 8·2 patients per bed). The shortage of beds is reflected both by the very high turnover, and also by the sharing of beds in the children's wards.

In addition to outpatient services at the hospitals, the Government Medical Service provides examination and treatment at static dispensaries throughout the island and from a few mobile dispensaries. Medical officers attend at stated times to see patients. The dispensaries carry stocks of the more commonly used pharmaceuticals and no charge is made for them.

The establishment of the Government Medical Service at the end of 1959 was for 86 full-time doctors, 1102 nurses, and 332 medical auxiliaries; but the actual number of full-time doctors in the service was only 74; there were also 209 vacancies for nurses, and 46 vacancies for medical auxiliaries.

The estate hospitals are provided by the employers; there are 27 of them with about 560 beds. They provide first-aid, and serious cases are transferred to public hospitals. They are staffed by 11 private practitioners.

The maternity and child-welfare services are provided in the towns by the Maternity and Child Welfare Society which runs 9 centres, and 15 are run by the Social Welfare Department in rural areas. In addition 1 mobile unit visits districts without clinics. The maternity and child-welfare clinics do not offer any family-planning guidance. In 1957 the Family Planning Association of Mauritius (now the Family Welfare Association) was founded, but it has been given no official support and operates on only a very limited scale.

A recent development has been a school health service providing free medical and dental treatment for primary schoolchildren.

There are about 57 doctors in private practice; 5 of these are paid to attend Government dispensaries part-time. Private doctors' prescriptions are dispensed by private pharmacists and the prices for these drugs are very high.

CURRENT PROBLEMS

A particular problem in Mauritius has been the phenomenal growth of the population. This has increased by half since 1945, due to a combination of a high birth-rate and a mortality-rate lowered by the eradication of malaria. At its present rate of increase the population can be expected to double by the 80s.

This large increase in the population aggravates the shortage of doctors. There is now only 1 doctor to every 4500 people in Mauritius. There are more medical students than there are doctors; for 200 students were studying medicine abroad at the end of 1959. It seems that this large number of students might resolve the shortage; but many of them will not return to Mauritius after qualifying since they find better conditions for practice abroad.

Another difficulty is the attitude of the Mauritians. In general, neither the potentialities nor the limitations of modern medicine are properly understood. A Mauritian who is ill will often seek advice from a number of different doctors, pharmacists, nurses, herbalists, and self-appointed lay experts; he will buy both modern drugs and traditional herbs, make vows to different deities, and visit shrines of more than one denomination. This pattern of behaviour offers singular opportunities for the sick to be exploited; and those who exploit suffering include doctors, nurses, and pharmacists. Many nurses take illicit charges from patients; some engage openly in private "medical" practice after their hours of duty. Owing to the shortage of doctors, it is inevitable that the sick should ask nurses, pharmacists, or indeed any person selling pharmaceuticals or medicinal herbs, to diagnose and prescribe. It is therefore not surprising that dangerous drugs are sold without a doctor's prescription. Nearly any preparation can be obtained and some are hawked from door to door. Such drugs as isoniazid and streptomycin are handed out indiscriminately. The cost of some drugs is extremely high; and some retail profit margins are at "the fantastic figure" of 300–400%. Chemists are alleged to offer free surgeries to doctors who will prescribe the drugs that they dispense. Private expenditure on drugs in Mauritius is very high by any standards, and amounts to nearly 2% of consumer expenditure. The corresponding figure in Britain is about ½%.

PROPOSED ACTION

Titmuss and Abel-Smith regard the provision of a family-planning service as their most important single proposal. They suggest that an immediate start be made with the facilities available and that the Government approach charitable foundations for assistance with a large long-term programme. Methods acceptable to the various religious denominations should be freely available to all and the aim should be a family averaging 3 children.

To overcome the shortage of doctors they recommend the recruitment of doctors from abroad as a short-term measure. For general practice these doctors would have to speak fluent French; but for specialists this would not be so important. Some system of exchange might be possible with a hospital in Britain or Australia, or secondment by one of the regional hospital boards in Britain for limited periods; or the Medical Research Council might set up a demonstration area in Mauritius on the lines of the one in Jamaica. But the main solution must come from recruitment of Mauritian doctors. Titmuss and Abel-Smith recommend that the Government scholarship scheme be extended, and some of them should be reserved for women. They suggest that Australia might be a better place to send the scholars, since opportunities for settling in practice are not so readily available. And they recommend that students financed by the Government should make some undertaking to return to practise in Mauritius or repay the cost of their medical education. In addition the Government should make it easier for doctors to return to Mauritius immediately after completing their studies; at present complicated formalities involve considerable delay: contracts should be offered to them and passages arranged before their final examinations.

Connected with the recruitment of doctors is the need for raising their ethical standards. Titmuss and Abel-Smith recommend the formation of a general medical council, and similar bodies for the nursing and pharmaceutical professions; and, in addition, an expert committee on the control of pharmaceuticals.

The most urgent health needs lie in the preventive health and welfare services, particularly for mothers and children. In 1958, of 26,303 births in Mauritius, 5449 took place at home without a qualified midwife or doctor. Only about half of the expectant mothers received antenatal care and very few received any postnatal care. Maternity and child-welfare services should be further developed. A campaign of health education to eliminate hookworm is necessary.

The domiciliary services should be expanded to reduce

the need for hospital beds, and the shortage of beds relieved by an effective chain of district hospitals. For mental defectives a combined institution and training centre should be built, and staff, in particular a psychiatric social worker, sent abroad to gain experience. As for the estate medical services, Titmuss and Abel-Smith recommend that the Government take over these hospitals and dispensaries. They consider that only exceptionally should compensation be paid.

A new family-doctor service should be started, giving free treatment to anyone registered with a doctor. The island would be divided into areas with several doctors offering services in each area. Patients would register with the doctor of their choice. This would be a salaried service; and doctors would be attracted to practise in the rural areas by providing them with free houses and inducement payments.

Titmuss and Abel-Smith recommend that hospital facilities should be free when recommended by doctors working in the service; private patients should be charged the full cost of any services provided, and pay-beds should be provided at the Government hospitals.

The dental service requires extension. All children and expectant mothers should receive free dental care. Dental assistants should be trained.

The new service should be renamed the National Health Service of Mauritius.

Medicine and the Law

Hormone Therapy not Marital Cruelty

A HUSBAND and wife were married in 1950. There was one child born in 1951. Soon after the marriage, the husband began to develop female character traits, and to dress as a woman.

In 1952 he consulted psychiatrists, and in 1954 he was sent to Guy's Hospital; eventually, he consented to undergo hormone treatment designed to accelerate and facilitate the development of female characteristics. In May, 1957, he left the wife, because he wanted to be a woman and could not endure living with her. Later he obtained employment as a woman clerk and held a female's National Insurance card.

In 1958, the wife's petition for divorce on the ground of cruelty was dismissed by Davies, J., who held that it was impossible to say that the husband's consenting, on medical advice, to undergo treatment for mental illness was legal cruelty.[1] After the expiry of three years from the date of the husband's leaving the wife, she petitioned for divorce on the ground of desertion. The husband did not defend the suit.

Judge ANDREW, sitting as a special commissioner for divorce, said that it was an extraordinary case, made even more extraordinary by the fact that this was the husband's second marriage, he having obtained a divorce from his first wife. The charge of desertion had been established, however, and the wife would be granted a decree *nisi* of divorce, the court's discretion being exercised in the wife's favour in respect of adultery committed by her during the marriage.

D. *v.* D. *Probate, Divorce, & Admiralty Division:* Judge Andrew, Feb. 22, 1961. Counsel and solicitors: M. R. Hickman (Alban P.B. Gould).

D. R. ELLISON
Barrister-at-Law.

1. See *Lancet*, 1958, ii, 1118.

In England Now

A Running Commentary by Peripatetic Correspondents

THE first cases of influenza are seen with a sinking heart:

" Mother's got it now! "

" We've got Susan in here on the settee, and the three boys in together upstairs."

" Could you look in next door as well please; the milkman says they are all down with it."

Patients' responses to the coming of flu into the home varies.

" Oh doctor, please come down, doctor, Frank's ever so queer, saying ' who is it swimming in the garden? ' I've just taken his temperature and I think it's 106! "

" Dear Doctor,

I would esteem it a favour if you would call at the above address at your very earliest convenience as my wife is in bed, and oblige, yours respectfully."

" Father's in bed with his chest, and we think it's 'flu as well."

Other patients manage without medical aid, and stagger down, pale and drawn, to the surgery when the fever has passed; or perhaps call in the doctor when it dawns on them, at the end of the second week, that Aunt Edith is really getting steadily worse.

Exaggeration of pre-existing mental patterns may complicate influenza. A paranoid patient finds that the television newsreader leers at him in a meaningful way. The melancholic knows that the end is near, and sends urgently for his solicitor to make a more up-to-date will before it is too late. The over-anxious curses his family for the fools they are, and has palpitation all night.

Doctors' responses also vary. One G.P. will plod steadily on, conscientiously examining each patient with an open mind, patiently listen to those " things they have always been meaning to ask him ", and be knocking on the doors of darkened houses at eleven o'clock at night. Another will rush into the house, taking the stairs two at a time, sum up the situation at a glance, issue certificates and prescription at a strategic distance from the patient, with a cheery " you'll be all right in a few days ", be on his way again inside five minutes, and be home for a quiet tea with his family before the evening surgery.

* * *

One day in the middle of the evening surgery I faced the grisly fact that I was arranging my life round my cigarettes. So I gave up smoking. Knowing that one addiction can replace another I was careful. My consumption of alcohol did not increase. My weight remained steady. But I soon noticed that things were different. One day the bookshelf where I keep the paperbacks burst at the seams and scattered its contents across the floor. I noticed, too, that I seemed to be making more trips to the public library and that I always seemed to have at least six books at a time on the go. On waking in the morning my first thought was to reach for my book. Only after a dozen pages or so did I feel able to face the world. I began to keep a book in the drawer of my desk and managed to take in a few paragraphs while patients were undressing.

At first I was delighted with my new habits. My knowledge of literature increased. Philosophy, belles-lettres, even the medical journals played an increasingly important part in my everyday life. The snags began to appear only when I was thoroughly addicted. For instance, I keep a book in the car for an occasional quiet read between visits, but I find it an effort to resist the temptation to read while driving. There are also social problems. While I am talking to anyone, if my eye catches anything in print, I am forced to read it, be it evening newspaper, religious tract, or private papers carried by my companion. I can only avoid doing this by staring fixedly and continuously at whoever is talking. This is sometimes, understandably, resented. I also find myself tempted to say to my guests: " Do read a book ", or, worse still: " What will you read—light novel or something stronger? I'm reading a thriller myself."

* * *

The sentiments may be those of the American State Department, but it was actually Alfred, Lord Tennyson, who having got a chopstick tangled up in his beard or something, huffed "Better fifty years of Europe than a cycle of Cathay." If Honest Alf had managed to survive the next fifty years of Europe, he would probably have given out with a groovy little lyric entitled, *Come into the garden, Suzy Wong*! Yet we medicos can learn from Old Cathay, cycles and all, because long before Suzy arrived, when the Dragon Kingdom was governed by the principles of Ying and Yang, and before they got rid of the flies, no wellbred Chinese gentleman would go sick-visiting looking his usual urbane self. Such tactlessness might remind the patient, if he needed reminding, how ill he was.

The nice sick-visitor, therefore, disguised his face, and let his demeanour sag into a semblance of ill health, getting into the part even further by taking some nauseating draught. There were even those so punctilious as to remove from their own persons such appendages as were missing from the invalid, a procedure which not only limited the number of their excursions but also rendered advisable prior inquiries as to the nature of the patients' afflictions. It was however in order, when visiting patients who had, for example, been guests of pirates and whose relatives had been a bit slow with the down-payments for ransom, to purchase for a few taels and take along a condemned criminal, tactfully trimmed into such shape as the occasion demanded.

One can only guess the effects of all this upon the hospital inpatient. All his visitors looked so much worse than he did, that it may have seemed hardly worth while going back home. On the other hand the physicians of Old China were much addicted to acupuncture and the lighting of small fires on selected areas of their patient, and he may have been eager to change places with his sick-looking sick-visitors.

* * *

Have you ever bought a mouth-organ? If not, have you ever wondered how the shopkeeper solves the dilemma of how to let the prospective customer try it without contaminating the instrument with his oral flora? I must confess that the problem had never struck me until I lately had occasion to buy a mouth-organ. The salesman produced several models. "Which tone do you prefer, Sir?" he asked, and held each instrument in turn in front of a little bellows, specially designed, and ran it back and forth gliding up and down the chromatic scale. As far as I could observe, the machine had only one defect—it did not reproduce the suck that plays so important a part in mouth-organ technique. When I have plucked up the courage I am going to go into a musical-instrument shop and ask to see a few tubas. My object, of course, will secretly be to see in operation the monstrous bellows that the king of the brass must need.

* * *

What are you going to do
With your Pilkington?
Are you going to buy a car
Or to travel far,
Or do you think it would be best
For once to be well dressed?
What about your wife
And your declining years of life—
Ought you to take the long view
With your Pilkington?

I know what I shall do
With my Pilkington.
I've worked the matter out
And must forbear to shout,
For, having paid the bills
And coped with glaring ills,
The balance will just be large
Enough for my surtax charge—
So that I shall take a short view
Of my Pilkington.

Letters to the Editor

REFRIGERATED VENTILATION FOR OPERATING-THEATRES

SIR,—As an engineer (without degrees) I did not attempt in my letter of Jan. 7 to discuss the simple engineering methods I assumed would be applied in a modern operating-theatre to eliminate unwanted heat. Our autoclaves and their accessories are all properly lagged and ventilated; but as yet I know of no device to prevent the emission of heat from the autoclave door (and interior), especially when it is opened to insert or remove instruments. I have furthermore operated with the autoclaves rendered inactive by turning off the steam (my instruments being sterilised elsewhere); but it made no difference whatsoever to the theatre temperature or humidity.

I have given much thought to the problems of theatre construction; but they are so numerous that it is impossible to discuss them in a letter. For instance, the effect of theatre height on temperature, &c.; explosions in low temperature theatres (they are much less likely and their relation to humidity is less critical); ventilating problems—(as Mr. Murley states [Feb. 4] the present "basic type of plant approved by the Ministry of Health is bound to worsen air conditions in certain types of weather"). I would say this type of plant is outdated and certain designs are bacteriologically dangerous and should be abandoned; but in fairness to the Ministry they must receive and take advice from ill-informed sources. I should be surprised if engineers have given such poor counsel—only doctors could be as muddle-headed as is evident in a study of the design and function of some of our new hospital empires. Architects must not be blamed as they invariably seek advice from the medical staff on requirements. Furthermore, it is inexpensive to warm and humidify ventilating air, but more difficult and costly to cool and dry it.

As a doctor, I mentioned some of the benefits of refrigeration in my letter of Jan. 7. In future, I would like to see a room laid aside for the cooling of patients (particularly the young) before operation and to which they are returned afterwards. Has anyone observed the effects of treating severely burned or injured patients by refrigeration? I think they would be pleasantly surprised at the results.

Here is a field for fruitful research at which I am battling on the threshold with only limited resources and time. What would John Hunter's reaction be in such circumstances—perhaps like the industrial giants who have kindly come to my help and offered to install the refrigeration plant at their own expense and without the need to wait long years for a committee to make a recommendation to proceed—"don't think, try the experiment".

Doncaster. DAVID AIKEN.

SURGEON AND ENGINEER

SIR,—Your annotation (Feb. 11) on the problem of cooperation between surgeons and engineers and the letters from Dr. Steel (Feb. 18), Mr. Charnley, and Dr. Scales (Feb. 25) stress a point which has long been of concern to me.

In this college we have had in our research programme since 1953 that part of biomechanics (a term which we were the first to introduce into this country) which deals with problems of the mechanics of the human body, replacement of bone by plastics or metallic prostheses, compatibility of living cells with implanted materials, and stress-bone formation relationship. During these years much friendly and fruitful cooperation with surgeons has been evolved. Although in the early years the major part of the engineering work had to be carried out single-handed, your readers interested in work in this field may wish

to know that there are by now many engineers of good academic standing who would wholeheartedly devote their research interests to the problems of biomechanics.

I am surprised at the comments made by Mr. Charnley about the reluctance of the engineers to cooperate with the surgeons. It was the Institution of Mechanical Engineers who organised a symposium on biomechanics in 1959—not the British Orthopædic Association. Mr. Charnley was invited to contribute a paper to that symposium in collaboration with two engineers. In my opening remarks on that occasion I stressed the need for cooperation between surgeons and engineers.

In 1956, when I gave three university public lectures on the mechanics of the human body and the behaviour of metals used in implants, invitations were sent to all those medical institutions whose members might be expected to be interested. The audience, with the exception of five orthopædic surgeons, consisted solely of engineers.

I can assure Mr. Charnley that if he wishes to employ on a permanent basis a qualified engineer with biomechanical interests I can give him at least three names and addresses. I suggest that this course would be an improvement on Mr. Charnley's proposal to rely on "the remarkably large number of fellows and members of the B.O.A. with natural mechanical talents". It takes as long to train a qualified engineer as to train a surgeon—my point is perhaps best illustrated by the "success" of the original Judet prosthesis and the various nailing techniques of the neck of the femur. Let us drop the amateur's approach and try, if not to understand the problems involved, at least to develop some appreciation of their existence.

It is essential for the surgeon to develop a dual approach to his problems. One is to apply existing knowledge to everyday cases as they arise, and the second is to embark on long-term basic research. It is in the latter that the engineer is of value. However, it seems in my experience that the surgeon is interested only in an immediate answer to his day-to-day problems and does not appreciate the necessity for further and often lengthy research.

With reference to Dr. Scales' letter, standards can be of value if based on experimental data and consequently if used with some understanding of their limitations. One can only standardise knowledge which already exists and one cannot produce standards by the mere fact of gathering several people into a committee.

Your annotation will have been of the greatest value if it arouses sufficient interest to further the course which I have been advocating for years—the setting up of a central research institute of biomechanics in this country.

Biomechanical Laboratory,
Civil Engineering Department,
King's College,
London, W.C.2.

J. M. ZAREK.

SIR,—Your annotation of Feb. 11 and Dr. Steele's letter of Feb. 18 make it clear that there are many people who would welcome an organisation, consisting jointly of medical men and engineers, whose purpose would be the pooling of technical knowledge in the wide area in which biology and engineering overlap.

The initiative has in fact already been taken, and the Biological Engineering Society, which has this as its main object, came into being last year.

The Society holds scientific meetings (the first was at the National Institute for Medical Research, Mill Hill, in October and the second at Guy's Hospital in January) at which papers are read and equipment demonstrated; and it provides opportunities for discussion of mutual problems between its members, who include engineers, physicists, biologists, and medical men. Affiliated membership is also available to scientific institutions and to commercial organisations. The council of the Society intends to establish a central information service, which will store and make available information on apparatus and components, fields of special interest, and current literature. A journal is also being considered.

Association with other bodies, as envisaged in your annotation, is included in the aims of the Society. Its honorary secretary is Dr. A. Nightingale, Physics Laboratory, St. Thomas's Hospital, S.E.1, from whom further information may be obtained.

Royal College of Surgeons,
London.

RONALD WOOLMER
President,
Biological Engineering Society.

THE MAMMARY SOUFFLE

SIR,—We were interested in your annotation of Feb. 25, having lately seen a case in which this sign was clinically relevant. Although unaware of the prior reference to it, we also called the murmur an "internal mammary souffle" in view of its association with lactation.

In 1959 a primipara of 20 with postpartum pyrexia was admitted to this hospital because she had mild anæmia, a palpable spleen and a localised, hissing, parasternal murmur in the second left intercostal space. Blood-cultures were sterile, and the fever settled without antibiotics in 14 days. The murmur was systolic extending into diastole, and it seemed to lag behind the heart-sounds. Firm pressure with a bell stethoscope temporarily silenced it. It was therefore exocardial and unlike a ductus-arteriosus murmur. It resembled a uterine souffle and we attributed it to increased flow in the mammary artery because the patient was lactating unusually freely. A month later the patient was well, but the murmur was unchanged. Lactation ceased after 12 weeks, and examination then showed that the murmur had disappeared. Her spleen was also impalpable, and its earlier enlargement was ascribed to iron deficiency. The murmur was not heard in 10 mothers subsequently examined after childbirth.

We thank Dr. K. M. McNicol for referring the patient to us.

Holy Cross Hospital,
Haslemere,
Surrey.

WALTER SPORR
G. A. MACGREGOR.

ATHEROSCLEROSIS AND CORONARY OCCLUSION

SIR,—The data in the second table (Coronary-artery disease, 1908–56) of Professor Morris and Dr. Crawford's letter [1] do not necessarily reinforce the hypothesis that atherosclerosis has declined in severity over the past forty to fifty years.

According to Professor Morris's previous analyses [2] of necropsy records at The London Hospital for the years 1908–13 and 1944–49, the severity of atherosclerosis had substantially declined in the forty years between these periods. It was assumed that the criteria for grading atherosclerosis had been essentially the same during both periods. This assumption is not a strong link in the argument and it can hardly be validated by now comparing the 1908–13 records from this hospital with the results of the 1954–56 National Necropsy Survey. With such a diversity of participants, the standards for grading atherosclerosis in the survey were probably less consistent with the 1908–13 standards than those in use at the same hospital in the 1944–49 period.

Another possible flaw in the argument is that the nutritional state of the subjects in the groups under review may have been quite different. Without the benefit of modern therapeutic agents and recent surgical advances, a patient in the 1908–13 era may well have died sooner after the onset of his mortal illness than his counterpart in the 1944–49 or 1954–56 periods. It has been shown [3] that the inanition of chronic diseases mobilises lipid from the atherosclerotic plaque. Thus the subjects in the 1944–49 and 1954–56 groups would have had a longer period of terminal malnutrition, in which to resorb atheroma lipids, than those of the 1908–13 group. Hence,

1. Morris, J. N., Crawford, M. D. *Lancet*, Jan. 7, 1961, p. 47.
2. Morris, J. N. *ibid.* 1951, i, 1, 69.
3. Wilens, S. L. *Amer. J. Path.* 1947, **23**, 793.

postmortem appearances in hospital patients might give the false impression that atherosclerosis in the general population is less severe nowadays than it was fifty years ago. In the future this problem could possibly be resolved by making a quantitative assessment of coronary atherosclerosis at necropsy in subjects who have died suddenly from trauma but who are otherwise healthy. A quantitative index for coronary atherosclerosis could well be adapted from that formulated by Dr. Holman and his associates [4] for atherosclerosis of the abdominal aorta.

In the face of a spectacular increase in the incidence of coronary occlusion during the last half-century, the suggestion that there has been a corresponding decline in the severity of coronary atherosclerosis is so unexpected that it surely requires more exact confirmation before it can be accepted. Even if the conclusion is correct, it cannot be inferred that atherosclerosis causing stenosis and occlusion of the coronary lumen is an essentially different disease to non-stenosing atheroma of the coronary wall. A small atherosclerotic lesion can precipitate occlusion just as effectively as generalised disease of the whole coronary vasculature.[1 5] The critical factor, which determines occlusion, is merely the direction of enlargement of the lesion—i.e., the degree to which the atherosclerotic process expands inwardly rather than up or down the arterial wall. Thus the underlying cause of coronary occlusion is still coronary atherosclerosis.

Laboratory of Pathology and Histochemistry,
National Institute of Arthritis
and Metabolic Diseases,
National Institutes of Health,
Bethesda, Maryland. C. W. M. ADAMS.

AN AID TO THE DIAGNOSIS OF HYPOFIBRINOGENÆMIA

SIR,—I was interested to read Dr. Aidin's letter (Feb. 25); he is to be congratulated on his attempt to help clinicians to remember what kind of bottles are required for the estimation of blood-fibrinogen and the performance of the clot-observation test. I feel, however, that he may be underestimating the ability and memory of the clinicians though I have no doubt that his aide-mémoire would sometimes be useful.

Most cases of hypofibrinogenæmia in obstetrics follow accidental hæmorrhage of the severe mixed or concealed variety; and, from a practical point of view, fibrinolysins rarely cause hypofibrinogenæmia. Few investigators have been able to demonstrate the presence of these substances. The diagnosis of hypofibrinogenæmia may be made when the conditions producing a fall of fibrinogen are remembered and the blood-fibrinogen is serially estimated or the clotting-time observed; these conditions are accidental hæmorrhage, retained dead fœtus or missed abortion, and amniotic embolism, in order of descending frequency.

I would strongly disagree that fibrinogen should be given when the blood-fibrinogen falls to 200 mg. per 100 ml., since this would mean that all cases of hypofibrinogenæmia would receive this treatment. There is adequate evidence that, provided intravenous oxytocics are given at the end of the second stage, there is rarely any further uterine hæmorrhage, even though there may be hæmorrhage from the needle puncture points in the skin. In general, fibrinogen should be given when operation is necessary, where there is extensive genital-tract injury, if anæsthetic agents which relax uterine tone are used, or if third-stage hæmorrhage continues in spite of the use of oxytocics, and when the fibrinogen level is below 100 mg. per 100 ml. If fibrinogen is required (and 1 American author found it necessary to give fibrinogen in only 7·4% of cases of accidental hæmorrhage), then it is better to use triple- or quadruple-strength plasma, since fibrinogen is difficult to get into solution and, since it is prepared from large pools of plasma, is said to carry a greater risk of homologous serum jaundice.

The clot-observation test is useful where facilities are not available for fibrinogen estimation. If a filmy clot develops, but disintegrates within twenty to thirty minutes, then the fibrinogen concentration of the blood is below 100 mg. per 100 ml. If no clot forms at all, then the concentration of fibrinogen is below 60 mg. per 100 ml. and, since hypofibrinogenæmia develops in from two to thirty-six hours (usually within six hours) of the onset of placental separation in accidental hæmorrhage, frequent clot-observation tests or fibrinogen estimations of the blood are required.

It should not be forgotten that a fall in the blood-prothrombin activity accompanies that in the fibrinogen. The prothrombin activity should also be estimated and, if necessary, intravenous phytomenadione (vitamin K_1) can be given.

Withington Hospital,
Manchester. L. S. DEANE.

DYSPNŒA DUE TO SUBCLINICAL AMŒBIASIS

SIR,—I wonder whether Dr. Hamilton and Dr. Lutwyche [1] would be kind enough to explain the mechanism by which *Entamœba histolytica* caused the dyspnœa complained of by the patient. If this is an allergic phenomenon, have they any evidence, other than the test of cure by drugs whose whole range of activity is still unknown, that the allergen was, in fact, *E. histolytica*?

Amœbiasis Research Unit,
Durban. R. ELSDON-DEW.

FIND THE LADY

SIR,—I refer to the distribution of the £9 million retrospective payments to hospital medical staff.[2] It is quite clear that the distribution scheme, recommended by the working-party as " extremely fair and reasonable ", has achieved the remarkable feat of favouring practitioners at opposite ends of the ladder. Consultants with merit awards and the lower grades are to receive surprisingly large sums, while consultants without awards come out relatively badly.

Why is this? At the special representative meeting last September, the Representative Body, relieved to know that the mysterious proposed scheme carried a guarantee (" extremely fair and reasonable "), quite properly approved the scheme, along with all the other recommendations, in good faith and without question. Some of us, unable to find the catch, had been shrewd enough to take the working-party's report to our accountants or group finance officers, only to find that even " our " experts could only scratch their heads and wonder.

Like schoolboys unable to solve difficult problems, those of us sufficiently interested can work backwards from the answers in an attempt to solve the mystery. The inescapable fact is that the formula inherent in the scheme has worked overtime for practitioners with low (pre Royal Commission) salaries who were given relatively large percentage increases by the Royal Commission. Fair enough, possibly, but why the fine dividends for our most highly paid consultants? The trick here is to split the awards away from the basic salary and each distinguished consultant is thus divided into two bits, a major and a minor. A questionable manœuvre and quite contrary to the Royal Commission's observation that " awards are thus simply a part of remuneration " (para. 214 of the report). The effect of this is dramatic. To take a simple example, the consultant with C award, and at the top of the scale, we find that in respect of his award he is to receive £408 as compensation for a salary increase (1956–60) of £250, but in respect of his basic increase of £800 he receives only £405. (I have adjusted the figure to the very top of the scale.)

It can be said, of course, that the awards did not receive any interim adjustments in 1957 and 1959. In total these payments for the C award would amount to £88 (5% of £500

4. Holman, R. L., Brown, B. W., Gore, I., McMillan, G. C., Paterson, J. C., Pollak, O. J., Roberts, J. C., Wissler, R. W. *Circulation*, 1960, **22**, 1137.
5. Crawford, T., Dexter, D., Teare, R. D. *Lancet*, Jan. 28, 1961, p. 181.

1. *Lancet*, 1960, ii, 1352.
2. *Brit. med. J.* Jan. 21, 1961, suppl. p. 15.

for thirty-two months, plus 4% of £525 for twelve months) and after correction for this (£408 minus £88) we are left with a very disturbing comparison:

C award.—£250 cash increase (50% over 1956 scale) compensated by £320 (128%).

Basic.—£800 cash increase (25·8% over 1956 scale) compensated by £405 (50·6%).

A little simple arithmetic here tells us that either the C award holder is being overpaid by approximately £200 or the man without award is to be grossly underpaid. Further, rather more complicated, arithmetic will convince most people that holders of A and B awards are also to receive handsome undeserved dividends, after allowance is made for the interim payments and, in their case, for salary abated in 1954.

The machine that produced this result can be classed as a one-armed bandit so far as I am concerned. Admittedly, the Representative Body pulled the trigger last September, but we did not know then that the thing was pre-set to deliver jackpots to a select few. Guaranteed goods are returnable when found to be shoddy.

This £9 million ought to be sent back for a re-deal.

Hull. K. W. BEETHAM.

MERCURY RESISTANCE AND EPIDEMIC STRAINS OF STAPHYLOCOCCUS AUREUS

SIR,—The antibacterial properties of mercuric chloride have attracted the attention of bacteriologists since Koch's classical experiments with spores of *Bacillus anthracis*.[1] Dr. Moore's paper [2] has again stimulated interest in this compound, and its use in identifying potentially epidemic strains of staphylococci.

The comments of Dr. Knights (Feb. 18) on thiomersal ('Merthiolate') prompt me to report a similar observation made with this compound.

Epidemic strains of pyogenic staphylococci, as judged by their growth on mercuric-chloride medium, uniformly failed to proliferate in thiomersal at a concentration of 1 in 145,000.

Miss J. M. Beavon kindly isolated the first strains used in this study.

Southampton. RONALD D. MACKENZIE.

STERILISATION

SIR,—We have been following the correspondence on hospital sterilisation services with great interest, but we were perturbed by Dr. Blowers' statement (Feb. 18) that a pathologist is usually the most suitable man to direct such a service, with the alternative possibility of surgeons, nurses, and engineers, and the pharmacist "bringing up the rear".

We consider that such a post calls for detailed knowledge, not only of the bacteriological and engineering problems which are encountered in sterilisation, but also of the characteristics of the materials which are to be sterilised.

The modern pharmacist, in contrast to some of Dr. Blowers' candidates, is eminently qualified to undertake such a task, which must include the complete control of syringe and instrument services, the operation of aseptic units, and *all* dressing sterilisation, besides more routine sterilisation.

A constant, rigid, personal control should be the maxim for a sterilisation-service director; and we cannot honestly believe that the pathologist, however eminent, can devote sufficient attention to running such a service in addition to his other duties, which are equally important.

J. I. HARRIS
R. L. HOBBS
B. J. MEAKIN
J. H. S. FOSTER
T. M. JEFFRIES.

Chapel Barton,
Nailsea,
Bristol.

1. Koch, R. *Mitth. a. d. k. Gesundheitsamte*, 1881, i, 234.
2. Moore, B. *Lancet*, 1960, ii, 453.

LOCALISATION OF INGESTED TELEMETERING CAPSULES

SIR,—Mr. Ridgway and Mr. Smith (Feb. 18) rightly pinpoint the importance of localising telemetering capsules in the alimentary tract.

There are 3 clues to the position of the capsule. The time since swallowing gives a rough estimate of the position; but even in normal fasting subjects, wide variations in transit-time make this guide of limited use. The actual information being transmitted by the pill is in itself of value, and in the case of pressure-sensitive pills is probably the most accurate index.

We have found that fluoroscopy with an image intensifier is more valuable than a series of films. Short periods of screening reveal the nature and rhythmicity of movements of the capsule in the intestine, and are often a valuable guide in differentiating between different areas of the intestinal tract. The judicious use of contrast media is helpful, particularly when the capsule lies in the right lower quadrant of the abdomen. Here the pill may be at rest for long periods, whether in the ileum or cæcum, and differentiation either by the motility pattern or by straight fluoroscopy may be impossible. In our experience, it is an advantage to have the colon and cæcum outlined by a soft barium shadow so that the capsule still contrasts with the background. This can be achieved by giving the patient some dilute barium before starting the study. Not only is the distinction between small and large intestine clearly made, but the ileocæcal valve can be accurately localised. In this way we have observed a capsule pass from the ileum into the cæcum while no rise in pressure was noted on the motility record.

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EVALUATION OF THROMBOTEST IN ANTICOAGULANT-THERAPY CONTROL

SIR,—We feel that we have been misquoted in the paper by Dr. Lempert and Dr. Poller.[1] They compared the results of Quick's one-stage test, the P & P method of Owren and Aas, the 'Thrombotest,' and a modification of the thromboplastin-generation test of Biggs and Douglas, to evaluate the suitability of these methods in the control of anticoagulant therapy.

They contrasted their findings with ours [2] and quoted us as follows: "Hicks and Bonnin (1959) have suggested that, in the majority of patients, depression of thromboplastin generation by anticoagulants runs parallel with the depression of Quick's test, but they gave instances in which this relationship was not close. In contrast, our results indicate that only in a minority is there good correlation between the two tests."

We agree with their findings. The important fact is that we did not use the thromboplastin-generation test of Biggs and Douglas, or any modification of it. We used an assay technique which is sensitive to changes which cannot be detected by the thromboplastin-generation test. Our method was based on the thromboplastin-generation screening test,[3] and was designed to measure collectively a reduction of the so-called "serum thromboplastic factors" upon which we believe the therapeutic effects of anticoagulant drugs may depend. It is therefore wrong to compare the results obtained with this test with any obtained by the methods used by Dr. Lempert and Dr. Poller.

We do not wish to detract from the value of the thrombotest. It was designed to provide a technique which was sensitive to reductions in the "serum thromboplastic factors," as was ours. The difference is that our technique is insensitive to reductions in factor VII, while the thrombotest takes this factor into account.

Institute of Medical and Veterinary Science,
Adelaide, South Australia. J. A. BONNIN.

Queen Elizabeth Hospital,
Adelaide, South Australia. N. D. HICKS.

1. Lempert, H., Poller, L. *Lancet*, 1960, ii, 1115.
2. Hicks, N. D., Bonnin, J. A. *Brit. J. Hæmat.* 1959, **5**, 194.
3. Hicks, N. D., Pitney, W. R. *ibid.* 1957, **3**, 227.

PHOTOMOTOR REFLEX AS AN INDICATOR OF CONSCIOUSNESS DURING CURARISATION

SIR,—The practice of using a muscle relaxant in conjunction with light general anæsthesia to produce suitable conditions for surgery presents a problem. The normal reflexes which indicate return of consciousness and appreciation of pain are no longer valid, because they involve voluntary muscle; hence, the surgeon may be operating on a patient who is conscious but completely immobilised by the action of the relaxant. This occurrence has been reported more than once, the most recent account being that of Graff and Phillips.[1] The experimenter holding a vivisection licence has a similar problem when he uses relaxants: if he is to interpret the pain clause effectively, he must have some means of judging whether an animal is conscious or not. Relaxants destroy the palpebral and pedal reflexes which are commonly used to assess consciousness and perception of pain.

The electroencephalogram can be used to assess depth of anæsthesia in a curarised man or animal, but it is not always available, and needs some skill in interpretation. Experiments have therefore been carried out to discover a simple method of assessing depth of consciousness in curarised dogs, the E.E.G. being used as a criterion of the activity of the brain. Pentobarbitone sodium, thiopentone sodium, and ether were used as anæsthetics, and succinylcholine chloride as the relaxant.

It was found that the photomotor reflex (change in size of pupil of eye with sudden change of light intensity), unlike the other reflexes commonly used for testing anæsthesia, gave a reliable indication of returning consciousness in presence of a relaxant. It became positive as the dog passed from stage III (surgical anæsthesia) to stage II (excitement). Premedication with atropine did not invalidate the reflex, provided that the dose of atropine was not more than 0·032 mg. per kg. bodyweight. It seems likely that this reflex would also be useful in human patients in similar circumstances. The work will be described in more detail elsewhere.

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HYPERSENSITIVITY TO MILK AND SUDDEN DEATH IN INFANCY

SIR,—I read with much interest the account of the work of Dr. Parish and his colleagues.[2] In the past eighteen months I have examined 7 " cot-death " cases at necropsy.

6 died between the fourth and the seventh week of life, and 1 at thirty weeks. All were boys. Their histories were identical: they were apparently in good health in the evening, and were found dead in the morning, usually with their face buried in a pillow. 4 were being fed on cow's milk; and there is evidence that the remaining 3 were not being breast-fed. 1 had been left sucking at a bottle of milk and had died after taking half of it. The respiratory passages were not obstructed in any child.

Although these children were all alleged to have been well before their death, closer inquiry revealed a somewhat different state of affairs. 3 had upper respiratory infections, and 3 had been feeding poorly and had either slight diarrhœa or vomiting. 1 had a well-developed cellulitis around a primary vaccination site.

In all the cases patchy atelectasis, congestion, and œdema of the lungs was observed. 2 also had some softening of the spleen suggesting a septicæmic process, but this was not confirmed.

The search for causative bacteria or viruses proved fruitless, but in 2 cases with mild gastrointestinal symptoms *Escherichia coli* 8603 (O group 55) was present in the gut. This was not thought, however, to be a likely cause of death in the absence of gross systemic effects.

In short, it is possible that most or all of these cases are explicable on the basis of a hypersensitivity reaction similar to that observed by Dr. Parish and his colleagues.

They also say that they are investigating whether this reaction is sufficient to cause death in infants. Is it possible that minor illnesses such as I have described play a considerable part in preparing the way for a fatal reaction?

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R.A.F. Hospital,
Akrotiri, Cyprus. A. W. MCCRACKEN.

1. Graff, T. D., Phillips, O. C. *J. Amer. med. Ass.* 1959, **170**, 2069.
2. Parish, W. E., Barrett, A. M., Coombs, R. R. A., Gunther, M., Camps, F. E. *Lancet*, 1960, ii, 1106.

THE CHROMOSOMAL CONSTITUTION OF THE STURGE-WEBER SYNDROME

SIR,—In a recent leading article [1] you suggested that in time it might be possible to associate many specific abnormal human phenotypes with the presence or absence of specific members of the normal chromosome complement. Implicit in this statement is the idea that genic unbalance determined by the aneuploid condition is the underlying cause of the abnormal development and hence of the clinical condition. We recently described a case of autosomal trisomy in association with the Sturge-Weber syndrome,[2] but suggested then that it was not possible from this single case to postulate a direct causal relationship between the trisomic condition found and the distinctive phenotype.

By courtesy of Mr. G. L. Alexander and Dr. A. White Franklin we have now been able to examine 7 further cases of this syndrome. 4 of these patients (cases 1–4 in the table) have already been fully described (cases 1, 3, 5, and 7 in the monograph of Alexander and Norman [3]) and the other 3 also fulfil the criteria used by these authors to diagnose the Sturge-Weber syndrome.

Short-term cultures of peripheral leucocytes were established according to the method of Hungerford et al.[4] Culture was terminated at three days, and the cell-suspension processed for chromosome study by the technique of Nowell et al.[5]

Chromosome counts and analyses were made on unbroken well-spread cells:

Case no.	*No. of cells observed*		*No. of cells analysed*	*Sex-chromosome constitution*
	46 chromosomes	47		
1	25	..	5 Normal	XY
2	31	..	9 "	XX
3	35	..	6 "	XX
4	22	..	5 "	XY
5	26	..	5 "	XY
6	38	..	13 "	XX
7	50	..	10 "	XY
8	..	43	14 All trisomic for no. 22	XY

The 7 new cases examined were all found to have a normal chromosome complement of 44 autosomes and a pair of sex chromosomes, the latter agreeing with the phenotypic sex. Dr. D. G. Harnden and Miss P. A. Jacobs have kindly allowed us to quote their findings in 2 cases of this syndrome which they examined cytologically. In both instances the chromosome complement was normal. The 2 cases reported by Lehmann and Forssman [6] also had a normal chromosome constitution.

In view of these findings we decided to examine the chromosome phenotype of the peripheral blood in the trisomic individual previously reported. This is of interest because it has been shown [7 8] that the chromosomal constitution of peripheral

1. *Lancet*, 1960, ii, 1068.
2. Hayward, M. D., Bower, B. D. *ibid.* p. 844.
3. Alexander, G. L., Norman, R. M. The Sturge-Weber Syndrome. Bristol, 1960.
4. Hungerford, D. A., Donnelly, A. J., Nowell, P. C., Beck, S. *Amer. J. hum. Genet.* 1959, **11**, 215.
5. Nowell, P. C. *Cancer Res.* 1960, **20**, 462.
6. Lehmann, O., Forssman, H. *Lancet*, 1960, ii, 1450.
7. Jacobs, P. A., Harnden, D. G., Court Brown, W. M., Goldstein, J., Close, H. G., MacGregor, T. N., Maclean, N., Strong, J. A. *ibid.* i, 1213.
8. Hayward, M. D. Unpublished data.

blood and bone-marrow may differ. This is not surprising since the hæmatopoietic tissue includes not only the bone-marrow but also the reticuloendothelial system. The results are presented as case no. 8 in the table; it will be seen that the trisomy of chromosome no. 22 was not confined to the bone-marrow.

The consistent presence of an abnormal chromosome complement is now well established in association with specific congenital defects. This is true in particular for certain sexual abnormalities. For instance, all the cases of chromatin-positive Klinefelter's syndrome so far described are male individuals of XXY constitution; similarly chromatin-negative females with Turner's syndrome are monosomic for one of the X chromosomes—i.e., are of the constitution XO. But a much less well-defined relationship exists with regard to abnormalities of the autosomes, as pointed out in your leading article. Only in one instance—in mongolism—has an adequate consistency been demonstrated between a specific phenotype and a characteristic trisomy. Such a close correlation has yet to be established for other autosomal abnormalities.[2] Indeed, in one instance [9] we can be sure that such a correlation does not exist. Here a phenotypically normal individual has been described who is trisomic for chromosome no. 19. Perhaps with some of the smallest human chromosomes a situation exists comparable to that in *Hyacinthus*. Here the systems of development and differentiation are so buffered against genic unbalance that individuals varying in chromosome number from diploid to triploid are found, but the development of the normal phenotype is very little disturbed.[10] On the other hand, evidence from *Drosophila* suggests that the reverse situation might also apply; for flies trisomic for any but the smallest autosome are completely non-viable.

There are four possible explanations for our finding of a trisomic individual with the Sturge-Weber syndrome:

(1) The trisomy of chromosome no. 22 is the cause of the characteristic phenotype; but the finding of 11 patients with a normal chromosome constitution would indicate that the syndrome can also be caused by other factors which may be genic or environmental in nature.

(2) The cause of the condition is environmental or genic, the trisomy being an accompanying—but not inevitable—phenotypic effect expressed at nuclear level.

(3) The trisomy bears no relation to the characteristic phenotype, but is merely a chance association of events.

(4) The extra chromosome is a supernumerary or B chromosome.

The existence of supernumerary chromosomes in other organisms is well known.[11] There appears to be no a priori reason why such supernumeraries should not be found in certain human populations; and indeed Kodani [12] claims to have observed them regularly in meiotic material from both oriental and European males. The somatic chromosomes of many of these individuals have now been examined; and apparently, except possibly in Fraccaro's case,[9] no B chromosome has ever been found; but the somatic elimination of such chromosomes cannot be completely ruled out.

When considering the autosomal trisomies (with the exception of mongolism) it is perhaps still justifiable "to shelter behind the circumlocutory hedging implicit in the words 'associated with'".[1]

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M. D. HAYWARD
B. D. BOWER.

SIR,—Hayward and Bower [13] recently assumed trisomy to be present for chromosome no. 22 in a case with the Sturge-Weber syndrome. Their cytological observations were based on bone-marrow cultures.

We have examined 2 patients with this syndrome by the skin-culture technique. The 1st was a 12-year-old girl with a "port-wine" nævus on the left side of the face, buphthalmos and blindness of the left eye, epilepsy, and a slight right-sided hemiplegia. X-ray of the skull showed calcifications with a gyral distribution typical of the Sturge-Weber syndrome.

The 2nd patient was a woman of 25; histological examination of an extirpated angioma from the left parietal lobe showed changes typical of the syndrome.

Skin-biopsies were cultivated by our standard cell-culture technique.[14] 30 apparently undamaged cells from each patient were examined. The majority of the cells had the normal diploid chromosome number. The chromosomes of 3 very distinct cells from each patient were matched and analysed in detail. All these cells showed a morphologically normal chromosome complement. Typical sex chromatin was present in 50–60% of the interphase nuclei.

Lehmann and Forssmann [15] also found a normal 46 chromosome complement in blood-cell cultures from 2 patients with the Sturge-Weber syndrome. It thus appears doubtful whether trisomy for chromosome no. 22 and this syndrome are related.

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K.-H. GUSTAVSON.

Neurological Clinic, Karolinska Institutet, Stockholm, Sweden.

O. HÖÖK.

SIR,—Hayward and Bower [16] reported trisomy for chromosome no. 22 in a case of Sturge-Weber syndrome.

I found a normal chromosome condition in 3 patients here with this syndrome, a girl and 2 boys. My results thus agree with those of Lehmann and Forssman,[17] who found a normal chromosome complement in 2 cases; in 1 of them the karyotype could be analysed, and was found to be normal.

2 of our patients are grossly retarded mentally; both have a unilateral facial nævus flammeus and suffer from convulsions.

The 3rd is normal mentally but has convulsions. All 3 have calcification of the cerebral cortex, typical of the Sturge-Weber syndrome.

Using the phytohæmagglutinin technique in 1 of them only one mitosis was analysable, but in the other 2 cases a number of satisfactory analyses were performed. All cells examined had $2n = 46$, and no deviation from the normal pattern was seen.

Department of Pædiatrics, University Hospital, and Institute of Genetics, Lund, Sweden.

BERTIL HALL.

THE PHILADELPHIA CHROMOSOME

SIR,—I think the work of Dr. Court Brown and his colleagues (Feb. 25) deserves admiration, but I disagree with the inference drawn from it in your leading article that chronic myeloid leukæmia cannot be due to deficiency of a circulating inhibitor.

You ask: "what causes the chromosomal defect?" In reply I should like to quote first Court Brown et al. arguing that the Ph^1 chromosome must bear genes controlling leucopoiesis, and then to quote just a few lines of my own article [18]: "If this . . . hypothesis is correct, we may suppose that the cell's sensitivity to inhibition is localised to a well-defined part of the nucleus—in genes or complexes of genes . . . long-continued serious deficiency of an inhibitor will produce secondary alterations in the corresponding receiving genes of conditioned tumour cells (in this case of the insufficiently restrained stem cells). Such alterations arise gradually in the nuclei of the stem cells, but increase progressively. If the white cells were only immature during the initial stage of the disease, they later become pathologically altered."

It is not known when exactly the alterations in the cells' corresponding genes come into being, but there is a probability that what is now called the Philadelphia chromosome will not

9. Fraccaro, M., Kaijser, K., Lindsten, J. *Lancet*, 1960, i, 724.
10. Darlington, C. D., Mather, K. *J. Genet.* 1944, **46**, 52.
11. White, M. J. D. Animal Cytology and Evolution. Cambridge, 1945.
12. Kodani, M. *Science*, 1958, **127**, 1339.
13. Hayward, M. D., Bower, B. D. *Lancet*, 1960, ii, 844.
14. Böök, J. A., Fraccaro, M., Lindsten, J. *Acta pædiat. Uppsala*, 1959, **48**, 453.
15. Lehmann, O., Forssmann, H. *Lancet*, 1960, ii, 1450.
16. Hayward, M. D., Bower, B. D. *Lancet*, 1960, ii, 844.
17. Lehmann, O., Forssman, H. *ibid.* p. 1450.
18. *Lancet*, 1959, ii, 400.

be found during the early stages of the disease. It may not be quite accidental that this chromosome has not been found in the three patients in whom the disease has pursued an unusually benign course, and that in most cases showing the Ph[1] chromosome, there were cells in which it was definitely not found.

Far from denouncing the role of inhibition, the new facts seem to confirm it and therefore, I think, the search for the missing inhibitor should be seriously continued.

Gorinchem, Netherlands. N. H. D. SCHÖYER.

TRANSLOCATION HETEROZYGOSITY IN MAN

SIR,—The report of what they interpret to be a translocation heterozygote by Prof. Böök and his colleagues (Jan. 21) leads us to recount our recent experience with an almost identical abnormal chromosome constitution.

From a six-week-old boy with multiple fractures, blue sclera, and other features of osteogenesis imperfecta congenita, 10 ml. of peripheral blood was withdrawn and cultured for 68 hours in pooled sera (Difco) by the method of Nowell and Hungerford.[1]

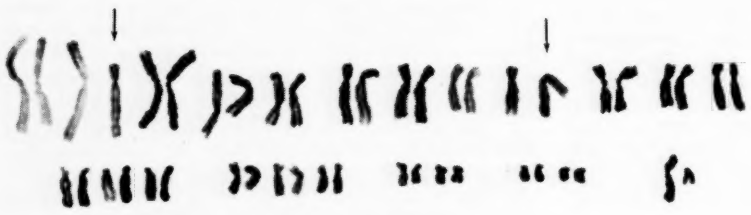

Fig. 1

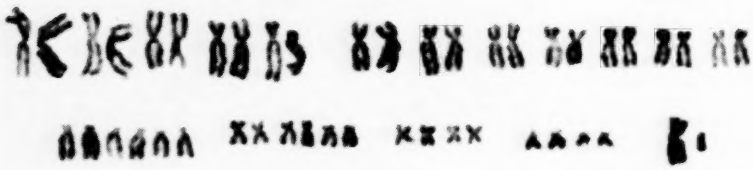

Fig. 2

Examination of the first few metaphase figures revealed that a substantial portion of the short arm of the second largest autosome appeared deleted. Subsequent attempts to align serially the chromosomes uncovered in each complement the presence of another abnormal chromosome too large to belong to the 6–12 group and with a centromere very close to the middle (fig. 1). Prof. Böök and his colleagues' interpretation of the abnormal karyotype they reported would certainly fit what we saw. We would agree that a reciprocal translocation involving the second largest autosome and a member of the 6–12 group would certainly account for the abnormal chromosomes in fig. 1. Of the 10 metaphase figures we analysed in detail, 9 contained these 2 abnormal chromosomes. We accordingly regarded this child as a translocation heterozygote.

To confirm this unusual finding, we took another 10 ml. of peripheral blood from this patient and again allowed the cells to grow in vitro for 68 hours, this time in the patient's own serum. We are disappointed to report that all metaphase figures this time revealed the normal male-chromosome constitution shown in fig. 2. We could only conclude that the 2 abnormal chromosomes observed in the first culture arose in vitro.

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Department of Experimental Pathology, City of Hope Medical Center, Duarte, California. CHRISTINA STENIUS
SUSUMU OHNO.
Children's Division, Los Angeles County General Hospital, Los Angeles, California. JACQUES NOWACK.

1. Nowell, P. C., Hungerford, D. A. *J. nat. Cancer Inst.* 1960, **25**, 85.

ASBESTOSIS AND ABDOMINAL NEOPLASMS

SIR,—Dr. Keal [1] analysed cases of asbestosis admitted to The London Hospital since 1948 in which other lesions were present. This was done to test an impression formed in that hospital in 1953 that "women suffering from pulmonary asbestosis had ovarian neoplasms more often than other women". No evidence is presented on the frequency of ovarian neoplasms in "other women", so that his case rests entirely on the reports of the hospital cases. As there is only one man with abdominal malignancy in this series I will offer no comments on the men mentioned in this study.

Any wide-ranging conclusion such as is drawn in the summary that, of the patients observed, 9 women and 1 man died with ovarian or peritoneal cancer and that this appeared to be more than a chance association, would seem to be invalidated by the narrow scope of the inquiry. A broader-based study would have been possible if the records of suspensions of women for asbestosis by the Pneumoconiosis Medical Panel had been followed up, and the causes of death noted in this group for the whole country or one substantial section of it. Only 3 of the recorded cases of abdominal growth were suspended, however, so even this source might not have been comprehensive enough for the purpose. In the whole group of 9 cases the diagnosis of ovarian cancer is only confirmed in the 1st case, it was considered probable in cases 2, 3, 4, and 6, and it was ruled out as a primary cause of death in cases 7, 8, and 9. Case 5 must be regarded as inconclusive.

In attempting to define the population which might be considered to be at risk to both asbestosis and ovarian and peritoneal cancer the exposure data given in table I should be examined. For 7 of the 9 cases, where it is alleged both conditions coexisted, the exposure periods were given as 1 to 7 years, in 1 case it was 21 years, and in the remaining case it was unknown. The period which had elapsed since last exposure in the known cases varied from 42 years in the case with 4 years' exposure to nil in the case with 21 years' exposure. The group in which to study the incidence of these conditions, either separately or in association, consists of all the workers exposed for 1 to 21 years in the past 46 years with survival up to the present. This would certainly be a large group of several hundred or even thousands. To make the task more manageable it might be profitable to study a group with a longer exposure period—say, 10 years—since this would be a smaller group and, with longer exposure, would be more likely to reveal any excess mortality from a specific cause. Ovarian and disseminated peritoneal cancer are common conditions and further proof is required of the related association of these conditions to asbestosis than that of the numbers of these cases which occurred jointly in the practice of a hospital in the neighbourhood of sources of asbestos exposure.

I have kept records of all the coroner's necropsies performed since 1930 in this area where there is a large asbestos manufacturing plant. These were done at his instigation where the persons concerned had been suspended for asbestosis or were likely to have developed the condition in the course of their employment. The total had reached 146 by the end of 1960; and of these 30 were women. No case of ovarian cancer or diffuse peritoneal neoplasm was found in any of these women. As a practitioner for 32 years in the neighbourhood of an asbestos works I can recall only 1 case of ovarian cancer in an

1. Keal, E. E. *Lancet*, 1960, ii, 1211.

asbestos worker, and this woman did not, as far as was known, suffer from asbestosis. If, in fact, there is substance in Dr. Keal's thesis, the findings in this area do not support it.

It would seem, also, that this article too readily assumes that the diagnosis of asbestosis by clinical and radiological methods is without error. In the first 3 cases reported there is good pathological evidence of asbestosis, but in the remaining 6 the diagnosis of asbestosis cannot be regarded as fully established. Even in case 9, where there was no known exposure, the necropsy findings are by no means conclusive. The limitations of radiological evidence in the diagnosis of asbestosis were well defined by Williams and Hugh-Jones [2]; they concluded that the radiological appearances of asbestosis were quite unspecific except in some advanced cases and that observer variability in grading asbestosis was great. The findings of asbestos bodies in the sputum is widely regarded as evidence of exposure and not as evidence of disease.[3–6] Conversely the absence of asbestos bodies in the sputum does not in any way invalidate the diagnosis of asbestosis; they are often absent in well-established cases.

It is noteworthy that while this paper indicates (case 27) that the figures relate to hospital admissions up to the end of 1959 no case with the suggested association of asbestosis and ovarian neoplasm has arisen since 1955. Perhaps the coincidence of these two conditions has, by chance, become rarer since that date.

Writers on asbestosis rarely mention the actual mineral inhaled during exposure. Three types of asbestos are commonly processed in this country; they are chrysotile, found in association with serpentine rock, and amosite and crocidolite which are extracted from amphiboles. As these materials are quite different chemically and have a different physical structure it cannot be assumed that exposure to one dust will necessarily have biological effects comparable with the others.

While clinical impressions are often the means whereby advances in medicine are initiated, it is also true that investigation has often proved that clinical impressions have been wrong. In my view, before the association of asbestosis and ovarian or peritoneal cancer can be proved to be other than fortuitious, much more evidence must be presented than is available in Dr. Keal's paper.

Rochdale. J. F KNOX.

REPRINTS

SIR,—Dr. Faulds (Feb. 11) is clearly to be congratulated on uncovering a practical and ethical dilemma of transcending interest to his fellow authors; but the argument must not become confused. The policy of requesting or sending reprints is not in question, but there are obvious misgivings on the propriety of the reprint card. I am surprised that so many of your correspondents are flattered by these missives, or can flatter themselves that their receipt is dictated by scientific necessity.

Proof that this is not the case is surely to be seen in their uneven geographical origin, but if doubts exist a visit to any of our large academic hospital libraries, preferably on Friday, should resolve them.

Friday is usually reprint day: and the visitor may observe, after coffee-time, many splendid young men, earnest and ambitious, eyes darting between title and summary and scribbling furiously. It is an admirable performance, and large numbers of cards can usually be dispatched—mainly to Sheffield, apparently—before lunch.

Since Dr. Discombe (March 4) seems to have completely shielded himself, he could hardly be expected to contribute to Dr. Faulds' problem other than by an excursion into the realm of psychological medicine. But the problem remains, and while discretion is necessary in each and every case Dr. Faulds could do worse than to give his priority to those who have taken as much trouble and expense as the author has in writing the article, and is requested to do in sending it; and an important additional reason is that in such instances there is a good chance that the article has in fact been studied.

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TREATMENT OF NASAL CARRIERS OF STAPHYLOCOCCI

SIR,—In his letter (Jan. 14), Dr. Rammelkamp stated that 'Soframycin' nasal spray, which we have demonstrated to be highly effective in suppressing nasal carriage of pathogenic staphylococci,[1] should not be used until it can be shown that the gramicidin content of the preparation is below a level which could cause micro-consolidation of the lungs.

Dr. Rammelkamp's comment is based on observations by himself and Weinstein [2] that 10 mg. of tyrothricin instilled into the nasal passages of rabbits caused extensive consolidation of the lungs. The tyrothricin in this study was composed of 80% tyrocidine and 20% gramicidin, and it is by no means clear which of the two was responsible for the toxic action on lung tissue. Indeed, it seems curious to attribute this toxic action to the smaller gramicidin fraction when the authors demonstrated that the tyrocidine component of tyrothricin was chiefly responsible for its toxicity for erythrocytes, leucocytes, and skin.

But the question of toxicity of soframycin for lung tissue may be resolved in a more direct fashion. The average volume of fluid expelled by the nebuliser is 0·1–0·2 ml.—sufficient for a single treatment. (The 2 ml. previously quoted is excessive for a single application.) 0·2 ml. contains 10 μg. of gramicidin; and it is expelled mainly in the form of large visible droplets.

We have attempted to determine the size-distribution of particles emitted by the nebuliser by spraying a saline suspension of *Staphyloccocus citreus* into a closed container directly over the inlet of an Andersen sampler.[3] Before atomisation, the sampler was already operating; and sampling continued for 2 min. thereafter. 2 cu. ft. of contaminated air was collected. The bacterial counts were made on 7·5% salt brain heart infusion agar (Difco) after 48 hours' incubation. 4 separate experiments were performed in which different volumes of bacterial suspension were expelled. The results are listed below

PARTICLE SIZE SPECTRUM OF ATOMISED SPRAY FROM A SOFRAMYCIN NEBULISER

Particle size (μ) (Andersen sampler)	*Staph. citreus* counts Experiment 1	2	3	4	Particle-size spectrum (as average % of total counts)
Stage 1: >8·2	40	96	165	198	23%
Stage 2: 5–10·4	89	120	211	165	28%
Stage 3: 3–6·0	102	188	180	193	31%
Stage 4: 2–3·5	49	99	86	98	16%
Stage 5: 1–2·0	9	11	9	11	2%
Stage 6: up to 1	1	2	0	0	0%

Although most of the large and rapidly sedimenting droplets escaped collection, it is evident that at least 60% of the fine particles emitted by the nebuliser are greater than 5 microns in diameter. Since it is generally agreed that particles greater than 5 microns do not penetrate the lower respiratory tract,[4 5] the maximum amount of gramicidin which could be delivered to the lung tissue would be 40% of the amount emitted—i.e., 4 μg. But the sampling technique did not permit the collection of the larger particles, which constitute the bulk of the fluid expelled. Thus it would not be unreasonable to suggest that about 2 μg. of gramicidin might be distributed over the human bronchial mucosa by a single application of soframycin spray. This is approximately one-thousandth of the toxic dose of tyro-

2. Williams, R., Hugh-Jones, P. *Thorax*, 1960, **15**, 109.
3. Gloyne, S. R. *Lancet*, 1932, i, 1351.
4. Simson, F. W., Strachan, A. S. *J. Path. Bact.* 1931, **34**, 1.
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thricin for rabbits when calculated on its gramicidin content or one five-thousandth when calculated on the total complex. In view of these findings, Dr. Rammelkamp's objection seems hardly justified.

We would like to add that we have treated hundreds of nasal carriers in St. Vincent's Hospital, Melbourne, without any detectable ill effects.

Department of Public Health,
Cornell University Medical College,
New York 21, N.Y. SYDNEY D. RUBBO.

SKELETAL FLUOROSIS

SIR,—It seems to me that Dr. Holman (March 4) has indulged in partial and/or selective quotation of other people's written statement.

He says: "Dr. Griffiths goes on to say that the absence of dental fluorosis in some of these cases is quite irrelevant." What Dr. Griffiths actually wrote was: "If in fact they emigrated into the area (or changed their water-supply) after the age of, say, 10 years, the absence of dental fluorosis is quite irrelevant to the point at issue."

Again, in his letter of Feb. 18, Dr. Holman refers to "the proposed permitted maximum of one part per million (which can result in objectionable mottling)". In support of this statement Dr. Holman quotes an article by Galagan and Lamson.[1] The level of one part per million was selected in this country because it does not cause objectionable mottling and I have no doubt that it would have been set lower if it did. A further perusal of Galagan and Lamson's paper is obviously indicated. In it (on p. 505) there is set out a figure in which it is quite clearly shown that "objectionable fluorosis" can occur at one p.p.m. or less, but the data refer to communities which have a mean annual temperature of about 70°F and the area to which they relate is described as one of the hottest inhabited areas in the United States. Dr. Holman makes no mention of this. The diagram also indicates clearly that in areas with mean annual temperatures of about 50°F (which is about what ours is here) "objectionable fluorosis" does not occur and I challenge Dr. Holman to produce, from the article which he has quoted, any statement which might justifiably have led him to infer that it does.

I frankly doubt whether partial and/or selective quotation is likely to meet with favour from those of your readers who seek from your pages to reach a correct judgment on the merits of artificial fluoridation of water-supplies at a level of 1 p.p.m. in this country. It may therefore be of assistance if I set out what in my view *is* the value of mottling as a sensitive indicator. First, it relates to communities, not individuals, and to water-borne fluoride. Where dental fluorosis does not occur or is only very mild, other signs of ill health due to fluoridation have never been shown to occur. I am aware that a few individuals have alleged that they can occur but I have yet to hear of any scientific validation of their views. Second, except where there has been obvious and major exposure to fluoride later in life other signs of ill health have not been soundly demonstrated except at quite high exposures—i.e., there is considerable safety margin if the appearance of dental fluorosis in a community is used as an indication of the upper permissible limit.

Finally, Dr. Holman says that "the fact is that . . . there has been no adequate scientific inquiry which proves that such a measure is either desirable or safe". It would have been more accurate had he said that in his view there has not been such an inquiry. This is not the view of an impressive array of scientific bodies headed by the World Health Organisation committee which have examined the evidence on fluoridation and have pronounced that it is safe and desirable. They would hardly have done so without evidence which in their view was adequate.

Health Department,
Watford, Herts. W. ALCOCK.

1. *Publ. Hlth Rep., Wash.* 1953, **68**, 497.

THE METRIC SYSTEM IN PRACTICE

SIR,—Unfamiliarity with the nomenclature of the metric system may have delayed the adoption of the system in this country. Perhaps the simple expedient of making present units equivalent to a convenient round number of metric units would be acceptable.

Thus, the present ounce avoirdupois is approximately equal to 28·3 grammes, the fluid ounce to 28·4 millilitres, and the standard inch to 25·4 millimetres. By making these units equal to 25 grammes, 25 millilitres, and 25 millimetres respectively, a British metric system could be evolved thus:

SOLID MEASURE

1 metric ounce	= 25 grammes.
1 metric pound	= 500 grammes = ½ kilogramme.
1 metric hundredweight	= 100 metric pounds = 50 kilogrammes.
1 metric ton	= 20 metric hundredweight = 1000 kilogrammes.

LIQUID MEASURE

1 metric ounce	= 25 millilitres.
1 metric pint	= 500 millilitres = ½ litre.
1 metric quart	= 1000 mill litres = 1 litre.
1 metric gallon	= 4000 millilitres = 4 litres.

LINEAR MEASURE

1 metric inch	= 25 millimetres.
1 metric yard	= 1000 millimetres = 1 metre.
1000 metric yards	= 1000 metres = 1 kilometre.
1 metric mile	= 1500 metres = 1½ kilometres.

The traditional names of weights and measures (ounce, pound, pint, quart, gallon, inch, yard, &c.) would be retained and if all weights, measures, and containers were marked with these equivalents, the system would be self-explanatory.

A simple British metric coinage could be devised with 3 bronze coins, 3 silver coins, and 3 paper notes:

Bronze halfpenny	= ½*d.*
Bronze penny	= 1*d.*
Bronze bit	= 2½*d.*
Silver fivepence	= 5*d.*
Silver shilling	= 10*d.* = 1*s.*
Silver halfcrown	= 25*d.* = 2*s.* 5*d.*
Red paper ten-shilling note	= 100*d.* = 10*s.*
White paper one-pound note	= 20*s.* = £1.
Blue paper five-pound note	= 100*s.* = £5.

A British shilling of 10 pennies would bring us into line with Continental practice where the monetary units retain their national names of franc, lira, peseta, mark, &c.

Edinburgh. J. SCOTT GREEN.

SIR,—The simplicity and advantages of the metric system are obvious and very well known to those living in the countries where it was adopted over a century ago.

The danger of shifting the decimal point to which Dr. Dawkins refers (March 4) can be considered as misplacing or miswriting a figure. The danger is no greater than in the archaic system under which somebody can inadvertently write gr. 3 for gr. 1/3 or vice versa; but this is failure of the individual and does not invalidate the system.

The solution that Dr. Dawkins proposes will undoubtedly bring about many more fatalities; taking his own example, 1·5 mg. becomes 1|5 mg.; but this can easily be read as 115 mg., thus giving a dose nearly 80 times too large, as against 10 times too large obtained by shifting the decimal point.

If the decimal point is to be superseded it is better to replace it by a horizontal stroke: thus 1·5 mg. becomes 1–5 mg.; or, as is sometimes done, replaced by a superscript comma: thus 1·5 mg. becomes 1'5 mg.

Winford Orthopædic Hospital,
near Bristol. J. M. SANCHEZ BAENA.

SIR,—As Mr. Whittet (March 4) and other pioneers of the inexorable campaign towards metric quantities in prescribing and dispensing have forecast, metric posology is nearly here to stay and this will be for the best.

I agree with Dr. Dawkins (March 4) that a real practical danger in the metric system is the insignificance of the "point". But surely his alternative of the stroke is even more open to misinterpretation. For the unconverted, 1|5 mg. is ⅕ mg. and the former will (while the native printer still has no alternative but to offer his odd fractions in this form), even in printed matter, be interpreted as 0·2 rather than 1·5.

It occurs to me that, in writing prescriptions at any rate, there is a more useful, easily written, and unequivocal symbol to replace the point—namely, the caret. In manuscript and typography this symbolises omission and draws attention to a halt in the train of thought as effectively as a point, and much more legibly. If, instead of 1·5, we were to write 1^5, unambiguity would be avoided, and the position of the often unidentifiable point would be beyond dispute.

However, as a pharmacist who has sometimes suffered at the illegible hands of physicians, I wonder if this practice can be inculcated any more easily in the prescriber than the simple exhortation: "Take your time, stop, and make a big point that can't be overlooked." Surely, in the end, careless writing is the common enemy against which no convention, apothecary's or metric, can be proof.

Woking,
Surrey. LLOYD E. DAVIES.

A SURGICAL DRESSING

SIR,—I have been much impressed by some dressings which have been used during the past eighteen months for a wide variety of surgical conditions in over 3000 patients at the Meath Hospital and County Dublin Infirmary.

These dressings consist of pieces of cotton tulle impregnated with 1% 'Viacutan' silver dinaphthylmethane disulphonate (methargen), and dyed yellow with tartraxine; they are supplied in plastic boxes.

The conditions treated included lacerated wounds of all kinds, trophic ulcers, compound fractures, chronic paronychia, skin-grafts, burns, radiation burns, varicose ulcers, decubitus ulcers, and operative wounds.

All were impressed by the quick cleaning and healing of wounds. Healing appeared to be faster with this dressing than with any other form of dressing tried, including vaseline-impregnated tulle.

In burns the dressing, left undisturbed for four to five days, relieved pain; infection was absent; and healing rapid.

Some illustrative cases follow:

CASE 1.—A colleague sustained extensive first, second, and third degree burns of face, neck, and both hands, which were treated with viacutan tulle. Healing was rapid and without complications.

CASE 2.—A girl, aged 10, had the terminal half of the distal segment of her right middle finger completely severed, with compound fracture of the terminal phalanx and avulsion of the nail. The wound and severed portion was cleaned with viacutan emulsion, sutured, and then dressed with viacutan tulle, which was left undisturbed for three days and then changed twice weekly. The texture of this tulle supports the wound edges; and in fractures of the terminal phalanx no splint is required. Systemic penicillin was administered. Notable features were complete absence of pain, no evidence of infection, and rapid healing. An almost perfect end-result was achieved.

CASE 3.—A man, aged 45, a furniture designer, craftsman, and pianist, had the top of his right thumb completely severed by lawnmower blades. Treatment was similar to case 2; and the result completely successful.

CASE 4.—A woman, aged 33, for two years had suffered from chronic paronychia of her left middle finger, treated by 3 different doctors and a surgeon who avulsed the nail without effecting a cure. Again the nail was avulsed; the swabs were examined and *Escherichia coli* found. Viacutan tulle dressings were applied for ten days only. Six months later the new nail was fully grown and infection had not recurred. It was noted that she now had a chronic paronychia of the right middle finger. She deferred having this nail avulsed for a further six months. After avulsion of the nail the positive organism was again found to be *Esch. coli*. The same treatment achieved a similar result.

CASE 5.—A woman, aged 39, had anterior poliomyelitis at the age of six months, and subsequently paralysis of the whole of the left lower limb. A trophic ulcer developed in 1954, and treatment was first sought in the Meath Hospital in September, 1958. All known forms of treatment, including various proprietary dressings and preparations, antibiotics locally and systemically, ascorbic acid in large doses, and vitamin D_2 were tried. Treatment with viacutan tulle first began on Aug. 4, 1959. Ten days later the ulcer, which was on the outer side of the mid-leg and $1^1/_2$ in. in diameter, had healed; and by Sept. 29 the affected area was completely epithelialised.

Side-effects have never been noted, even after prolonged application. I feel that viacutan tulle dressing merits wide acceptance as a general utility dressing for a host of surgical conditions. All burns admitted under my care are now treated with this material, which I regard as the premier dressing, after trying many other forms of treatment with less good results.

I thank Messrs. Ward, Blenkinsop & Co., Ltd., for the supply of 'Viacutan' tulle.

Meath Hospital and County
Dublin Infirmary, Dublin. DOUGLAS MONTGOMERY.

INTUSSUSCEPTION IN INFANCY

SIR,—I read with interest the paper by Mr. Ross and Mr. Potter (Jan. 14).

I was once fortunate in seeing an intussusception actually take place during an operation, and it appeared that the mechanism is due to the excessive contraction of the longitudinal muscle in a portion of bowel which is in vigorous peristalsis. The bowel is drawn up into a ring which looks rather like a de Pezzer catheter, and then the proximal edge passes through the distal portion.

I have also had a case of intrauterine intussusception where the baby was born with about 12 inches of gangrenous small bowel due to an intussusception of the jejunum, which was successfully resected.[1]

I feel quite certain that the factor exciting intussusception is excessive or irregular peristalsis of the bowel; and this may be due to many causes of which infection may be one.

Newcastle General Hospital. STEWART FEGGETTER.

SIR,—I was extremely interested in the preliminary communication by Mr. Ross and Mr. Potter (Jan. 14). Over nearly thirty years I have observed enlarged mesenteric glands in infants with intussusception, and have always believed, and taught, that these were in some way the cause and not the result of the intussusception.

I noted such glands in over 90% of the cases I operated on. The glands are usually clustered in the ileocæcal angle; and within a few hours of the onset of symptoms I have often seen them as large as beans. This is a strong indication that the glands were enlarged before the intussusception started. In addition gross thickening, due to œdema and congestion, is strikingly limited to the terminal ileum, the part richest in lymphatic tissue. In the only case in which it was possible to take sections after death, the inflammatory congestion was found to be localised to the lymphatic tissue of the terminal ileum. Many microscopical studies of the glands of the ileocæcal angle have confirmed the presence of lymphatic hyperplasia.

It will be of great interest, as the authors suggest, to

1. Feggetter, S. *Brit. med. J.* 1954, ii, 1335.

await the results of further work on adenovirus infection in children with intussusception.

Southampton Children's Hospital, Hampshire. L. AYLWIN RICHARDSON.

EXTERNAL CARDIAC MASSAGE

SIR,—Dr. Healy (March 4) need not feel that his case of cardiac arrest was in any way inefficiently conducted. Cases of this kind inevitably occur out of the blue and if the diagnosis can be made and effective action taken within a minute or two, one need not feel in the least abashed about failing at the same time to record the precise duration of cardiac standstill.

While regarding a blow over the heart as a perfectly reasonable procedure in cardiac arrest, my own experience of 3 successfully treated cases [1 2] (following intravenous anæsthesia, acute pulmonary œdema, and coronary thrombosis respectively) leads me to suggest that when confronted with this emergency, the practitioner should as a first-aid measure press firmly and repeatedly on the front of the patient's chest. Thus 3 aims are subserved:

(1) The heart is compressed and the circulation is maintained in the direction permitted by the heart-valves.

(2) The circulating blood is partially oxygenated, since repeated pressure on the front of the chest would appear to be a method—albeit inefficient—of achieving artificial respiration.

(3) If the heart is imagined lying like a flaccid balloon on the front of the vertebral column, then sudden vertical pressure on it will increase its internal pressure and therefore its muscular coat will be, stretched. The muscular coat, when stretched, will, one hopes, respond by contracting and thus restoring normal heart-beat. (Hence the value of a blow over the heart.)

This first-aid treatment is as easy as it sounds, and as pointed out elsewhere,[3] may be continued for a long time if an efficient method of artificial respiration is available.

Lowestoft. N. B. EASTWOOD.

ORAL PROGESTOGENS

SIR,—We entirely support Mr. Klopper and Mr. Macnaughton (Feb. 11) in their view that a double-blind trial of the treatment of habitual abortion is long overdue. Apart from testing the efficacy of all the new oral progestational compounds, more scientific evidence is obviously required to support or disprove the belief that progesterone-lack is a factor in patients who habitually abort.

Surely the criterion for including patients in such a trial should be a deficiency of progesterone in the pregnancy under observation, and not merely a history of 3 consecutive abortions. We have found that the quickest and simplest method of assessing progesterone is by vaginal smears. An absent or poor progesterone response is easily recognisable and would seem to provide a satisfactory basis for carrying out a double-blind trial with dummies and one or more of the progestational compounds. For instance, we have had patients with histories of previous abortions with perfectly normal pregnancy smears throughout gestation, and who had normal deliveries without any form of hormone therapy. Surely it is this type of case which confuses the results obtained from trials based on the history alone.

Mr. Klopper and Mr. Macnaughton state that they have serially assayed pregnanediol excretion in 54 women with a history of previous abortion, 8 of whom aborted. They do not, however, give any indication as to how their findings were correlated with the clinical progress of these pregnancies.

Endocrine Cytology Unit, Chelsea Hospital for Women, London, S.W.3. F. OSMOND-CLARKE M. MURRAY.

1. Eastwood, N. B. *Brit. med. J.* 1960, i, 646.
2. Eastwood, N. B. Data communicated to College of General Practitioners.
3. *Brit. med. J.* 1960, ii, 1582.

Parliament

Suicide Bill

INTRODUCING the second reading of this Bill,[1] Viscount KILMUIR, the Lord Chancellor, said that for some time it had been widely felt to be inappropriate that we should continue to regard suicide as a criminal offence. The suicide had put himself beyond the reach of punishment; the existence of the offence in our criminal law had not proved an effective deterrent to others, as over 5000 suicides a year were known to the police in England and Wales. The continuing criminal character of the conduct did nothing but add to the distress and pain of the relatives and friends of the deceased. For these reasons the Government had concluded that the criminal offence of suicide should be abolished.

Attempted suicide presented rather different problems. Like suicide itself, attempted suicide had none of the characteristics of criminal conduct. On the contrary, it was often a sign that medical and social help was wanted. For many years the practice of the police had been to institute criminal proceedings only where there was no relatives or friends willing to give help and accept responsibility, or where the person making the attempt had refused to accept help from those about him. Thus in 1959, there were 4980 attempts to commit suicide known to the police, but criminal proceedings were brought in only 518 cases. The only justification for retaining the offence had been as a means of bringing before the courts, and perhaps helping, those who had made suicidal attempts.

Besides the 5000 or so attempts which came to the notice of the police every year, it had been estimated that a further 25,000 attempts were made and concealed because of the social and criminal stigma to the act. Criminal proceedings were not the best way of dealing with people who were in distress or disturbance of mind. The Home Office had concluded that attempts to commit suicide should also cease to be offences against the criminal law. The only problem had been the practical one of whether alternative and more appropriate methods were available for providing help where it was needed. Arrangements had been made to ensure that persons who were brought to hospital having attempted suicide were examined by a psychiatrist, who could consider whether treatment or supervision was needed. Under the provisions of part IV of the Mental Health Act 1959, it was possible to detain for 28 days' observation a person who appeared to be suffering from mental disorder and who ought to be detained for his own health or safety. This short period of compulsory detention could be initiated either by the application of the nearest relative or by that of a mental welfare officer. In these circumstances it had been thought possible and right to introduce this reform in the law.

Mock Milk

On Feb. 28 Mr. GEOFFREY DE FREITAS prayed against the new regulations [2] which are being introduced on the use of skimmed milk to which vegetable fat has been added. He did so not because this form of milk, which has been known as "filled" milk, was in any way unwholesome, but because the regulations did not require a caterer to disclose its use in cups of tea and coffee, and thus offered inadequate protection to the consumer.

Sir LESLIE PLUMMER said that in his view the regulations would allow a manufacturer to advertise filled milk as benefiting the overweight man who had too much cholesterol. The medical profession might believe that too much animal fat led to an excess of cholesterol but they were not certain.

Mr. CHRISTOPHER SOAMES, Minister of Agriculture, Fisheries, and Food, thought that criticism of the regulations was based on a misconception. They were in fact designed to protect the consumer in relation to a new technical development in the food industry. The product, when sold in powder form to be

1. See *Lancet*, Feb. 25, 1961, p. 447.
2. S.I., 1960, no. 2331.

used by caterers in cafés and other catering institutions, was more expensive than ordinary skimmed milk powder and cheaper than whole milk. It could be used to replace skimmed milk powder in cooking and to replace liquid milk in drinks. Its second use was in foods sold at higher prices than whole milk. Some were baby foods. There were cases where the Government's medical advisers agreed that it might be useful. The makers recommended its use in the prevention or treatment of coronary disease, but medical opinion on the soundness of these claims was divided.

There was nothing nutritionally defective about the product, nor was there any question of it being harmful. The Government might, therefore, have taken the line that the general provisions of the Food and Drugs Act were sufficient to protect the consumer, and that the product should find its own level. But they recognised that the public might be confused as between this product and whole milk, so they decided, despite the fact that it was unobjectionable from the nutritional point of view, that the public should be protected by specific regulations as well. What did the regulations do? Firstly, this product had commonly come to be known as "filled milk". The Government felt that this name might give the erroneous impression that it was ordinary milk, and so the regulations made it compulsory for the words "skimmed milk with non-milk fat", or certain equally specific and not more attractive alternatives, to be printed on the labels and in the advertisements of the product. The regulations prohibited the labelling and advertising of this product, and of drinks containing it, in a manner suggestive of milk or anything connected with the dairy interests. There was a further provision to require labels for these products to carry the words "Unfit for babies" or "Not to be used for babies", except in certain specified cases which were suitable for baby foods. He thought that the regulations provided valuable and fitting safeguards for the consumer. The suggestion that canteens and catering establishments should display a placard that they used the product, though superficially attractive, would not be effective.

On a division the prayer was denied by 201 votes to 152.

Blood-tests in Affiliation Proceedings

ON Feb. 28 in the House of Lords, Lord AMULREE introduced the Affiliation Proceedings (Blood Tests) Bill which seeks to make blood-grouping tests available to magistrates' courts to assist in the solution of affiliation cases. Such tests are being used increasingly in England, but only when the parties agree to this course and are prepared to meet the cost of the investigation. The Bill gives magistrates' courts power to order blood-tests to be carried out by an approved expert. The order may be made either on the initiative of the court or on the demand of the mother or the accused man. The Bill provides for the cost of blood-tests to be met from public funds, if the court so decides. It also lays down that samples must be collected by a doctor, but permits non-medical people, approved by the Lord Chancellor, to carry out the tests.

N.H.S. Bills and The Guillotine

On March 6, Mr. R. A. BUTLER, the Home Secretary, introduced a motion, which was carried, limiting the remaining proceedings on the National Health Service Contributions Bill and the National Health Service Bill.

QUESTION TIME

Medical Education

Mr. KENNETH ROBINSON asked the Minister of Health if he would advise the setting up of a Royal Commission on medical education in Great Britain.—Mr. POWELL replied: No, Sir. The General Medical Council, which is responsible for maintaining the standards of medical education, published revised recommendations on the medical curriculum in 1957, after extensive consultations with the other bodies concerned with medical education and practice. I understand that it has recently received from medical schools reports on the implementation of these recommendations and that these are being considered. Mr. ROBINSON: Even allowing for these recommendations, is not medical teaching in this country now many years behind that in the United States and many European countries, and does the Minister realise that that view is shared by many younger doctors and medical students and most psychiatrists because it is particularly backward in the teaching of psychological medicine? If any improvement is to be made, must not some initiative come from him, because it is no use leaving the matter in the hands of just those leaders of the medical profession who are responsible for the out-of-date curricula which we have? Mr. POWELL: The responsibility of the Minister of Health for medical education is necessarily and deliberately extremely limited. I have no reason to doubt that the General Medical Council's recommendations took full account of the need for expansion in psychological medicine, and this will be reflected in the results it is now considering.

Mr. L. ABSE: Does the Minister recognise that so laggard is medical education in Wales that, despite more than a decade of pressure from the regional hospital board, we are still without a chair and department of psychiatry? Will he continue to take action to carry forward what has been indicated as necessary by the Minister for Welsh Affairs and ensure that medical students in Wales can have a proper education in psychiatry? Mr. POWELL: I think that that is not a question for me.

Medical Care of Epileptics

Mr. G. W. REYNOLDS asked the Minister of Health what progress had been made in carrying out the recommendations made in 1956 by the Cohen Committee that each regional hospital board should establish a diagnostic and treatment clinic for epileptics per 1 million of its population, and a long-term treatment and rehabilitation centre per 2 million; that long-stay hospital units should be established for epileptic children with exceptionally bad behaviour disorders; that in larger towns hostels should be established for epileptics who were employed but needed continuing medical supervision.—Mr. ENOCH POWELL replied: This report was commended to hospital authorities who have to consider its recommendations in the light of the other needs for which their plans must provide. Diagnostic facilities, either at special clinics or as part of general neurological or psychiatric services, have been provided in all regions. Some boards have been able to provide separate wards for short or longer-term treatment. It has not yet been possible to provide special units for epileptic children with behaviour disorders or hostels for employable epileptics in need of medical supervision.

Remuneration of G.P.s

The average gross payments per head from public sources to be received by general practitioners under the new settlement are estimated approximately as follows for 1961–62:

	£
1. From executive councils	
(*a*) Capitation and loading payments	2970
(*b*) Temporary residents fees	55
(*c*) Initial practice allowance and other payments from the central pool	10
(*d*) Mileage allowance	90
(*e*) Payment for maternity medical services	300
(*f*) Payment for drugs	135
(*g*) Reimbursement of training grants and allowance for the supervision of trainee practitioners	20
(*h*) Payment for sight-testing	5
	3585
2. From hospital authorities	75
3. From local authorities	55
4. From Government departments	35
	£3750

In addition, £1 million, representing an average of about £45 per head, is being temporarily reserved for further discussion. The allowance for practice expenses cannot yet be finally determined. Exchequer superannuation contributions, which are no longer taken into account in the central pool calculation, are provisionally estimated at about £230 per doctor for 1961–62.

Obituary

HAROLD ARTHUR THOMAS FAIRBANK

Kt, D.S.O., O.B.E., M.S. Lond., F.R.C.S.,
Hon. M.Ch. Orth. L'pool

Sir Thomas Fairbank, whose death on Feb. 26 we announced last week, had a life that was rich in ideas and achievement. He was a leader and explorer, a teacher and student, and above all a scientist in clinical medicine. The memorials of most surgeons are contained in the mortal bodies of their patients and there are many thousands who have reason to be thankful to Sir Thomas, directly or indirectly. But his more lasting memorial will be his teachings and his writings—masterpieces of lucid exposition, culminating in his great *Atlas*.

H. A. Thomas Fairbank was born in 1876, the son of a general practitioner in Windsor. He was educated at Epsom College, and qualified from Charing Cross Hospital in 1898. He also took a dental diploma, for he had originally intended to become a surgeon-dentist. But his experiences as a civil surgeon in the South African war turned his interests to surgery, and after he returned to London he took the F.R.C.S. in 1901 and the M.S. in 1903. During these years of preparation he was senior resident at The Hospital for Sick Children, Great Ormond Street, and began the studies from which he made his great contributions to the disorders of childhood. At this early stage he was much influenced by Arbuthnot Lane and his no-touch technique which Fairbank continued to practise and teach throughout his active life. In 1903 he first saw Lorenz treat a child with congenital dislocation of the hip (a relatively neglected condition in those days), and within a few weeks, while still a clinical assistant, he had himself carried out a similar reduction. This condition remained a never-failing subject of his teaching and conversation, and his Lady Jones lecture in Liverpool in 1929 is a penetrating study of its anatomy.

Stoneman

Sir Thomas was one of the great generation which included Elmslie, Trethowan, Bankart, and Bristow, but with his appointment to Charing Cross in 1906 he was the first to become an orthopædic surgeon with no other clinical commitments at a London teaching hospital. He was also on the staff at Great Ormond Street, to which in 1913 he became senior surgeon. Of the years he spent there a colleague recalls:

" Fairbank taught, chiefly by example, the skilful handling of children, the careful management of orthopædic appliances, and neatness and attention to detail. He generally managed through gentle but firm persuasion to get his own way, and this was illustrated by his success in breaking the long tradition by which all outpatients were seen by assistant surgeons and only senior surgeons had inpatients. Throughout his time at Great Ormond Street Fairbank shared with his assistant both inpatient beds and outpatient follow-up clinics—a practice which is now usual throughout Great Britain."

Before the 1914–18 war, Fairbank toured North America and met Whitman, Lovett, Murphy, Goldthwait, Osgood and Abbott. He had been a keen Territorial officer and when war broke out he and several other junior consultants were drafted to a field ambulance.

One of them, J.T., later wrote: " All of us looked up from the beginning to this man who seemed to us to be the essence of wisdom, kindness, common sense, and unselfishness." He recalls how Uncle Tom showed his foresight and organising capacity by collecting funds to buy seven motor ambulances, specially built for the work, which enabled the unit to get overseas quickly. In 1915 the unit was transferred to Greece (without their excellent vehicles), and Fairbank established what we would now call a rehabilitation unit—the first of its kind overseas. J.T. continues: " He overworked himself keeping a constant check on the wounded from clearing-stations to base hospitals. He invited his forward surgeons regularly to the base to see for themselves what happened to their patients and to hear his commands. This kind of ever-watchful sanity was the special quality of his work. Informed as it was by his great surgical and orthopædic knowledge, experience, and judgment, there was nothing in it, nor in him, that had any quality of the showman. His was a personal service to the sick and wounded conducted by willing deputies. The necessary result was that, while he did not spare himself the work did not spare him either."

After his return to civil practice in 1919 Fairbank was invited to become senior orthopædic surgeon to King's College Hospital and he resigned from Charing Cross Hospital; but he continued at Great Ormond Street until 1928, and he had a hand in the development of its country branch at Tadworth, Surrey. He also was a consultant to Queen Alexandra's Hospital, Millbank, and he did much clinical work there and at the Cambridge Hospital, Aldershot. In 1924 his help was sought by Sir Henry Gauvain for the Lord Mayor Treloar's Hospital at Alton, and Fairbank gave great service there, particularly in the training of surgeons.

He had been appointed to King's to found a department of orthopædic surgery, and he also started one of the first fracture clinics. Once again he laid great stress on the need for members of the senior staff to work and teach in the outpatient clinics, and he cultivated a close liaison between the orthopædic and physiotherapy departments. Of the days at King's H. L.-C. W. relates:

" In the operating-theatre, Fairbank dressed in white overalls, and wore long black shiny top-boots, and a visitor once remarked that his outfit, together with his distinguished appearance, made him look like the Duke of Wellington; and so indeed he did. There was always a small electric steriliser near the instrument table, in which the ' business ends ' of the instruments were dipped from time to time, and from which plates and screws were transferred direct from boiling water to patient. Metallic inserts were never allowed to lie about on the instrument table before use. If these operations took a little longer, an exceptionally low sepsis-rate was the reward for all this extra care. His wide knowledge, phenomenal memory, and meticulous attention to every detail of treatment were exceptional, but it is for his qualities as a man that we at King's will remember him.

" Above all, he was honest with himself and looked for the same quality in others, and his high integrity shone as an example: courteous and kind, so that the most junior house-surgeon was never forgotten and always had a word of encouragement, even in the midst of an important gathering; respected at all times by his patients, who when growled at and deservedly called ' a fool ', liked him all the more; known by everyone as H.A.T., Fairbank was loved by generations of King's students in a way that few others have been. At his farewell lecture in 1936 his car was intercepted by a large band of students before it reached the hospital gates, and a rope stretched across the road to bring it to a halt. The rope was attached to the car, which was towed by hand to the front entrance. Fairbank entered the hospital beneath an archway of bones. The lecture-theatre was decorated with streamers and the lecture-bench was a mass of flowers. At the end of the lecture, students presented him with a silver replica of the shoulder abduction splint which he had designed. This was

indeed a memorable occasion which we all thought marked the end of his association with us, but when war-time duties called others away, how glad we were to see him return to help in the outpatient department, and sometimes to operate again."

The inter-war years were a period of intense clinical activity, and Dudley Buxton, who joined him at King's in 1922, has written charmingly of the happy work-a-day atmosphere at Fairbank's home in Harley Street, where for so many years he was helped devotedly by Sister Bradbury.

"Living at Harley Street he was engaged in a large consulting practice and doing regular work at Treloar's Hospital and Millbank. He was visiting King's and Great Ormond Street on the request of his friends requiring help, usually with less common skeletal diseases. From many parts of the country he was being requested to study reports and radiographs of such conditions not well recognised. Evenings were spent collating information on these and writing. Holidays were medical meetings and short periods of fishing, and weekends at The Mill. This lovely house in a bend of the river must have given him, his family and their visitors great relaxation and was the envy of many."

In 1939 war again interrupted Fairbank's normal practice. As consultant adviser in orthopædics to the Ministry of Health, he organised the E.M.S. orthopædic services, and later, as chairman of a committee of regional and Service advisers, he had to hold the balance between the demand for staff by the Forces and the civilian needs on the home front.

H. P., who was appointed consultant adviser to work with him in the expansion and supervision of the orthopædic services of the Emergency Medical Service, writes:

"Together we visited the regions regularly, and between our monthly conferences in London we were continuously in touch through an interchange of letters. As I write these words of farewell on the passing of a very dear friend and colleague, I have before me a file of this war-time correspondence containing many letters in his own handwriting, full of wisdom and commonsense. It was sometimes our unpleasant duty to tell certain hospitals, then independent institutions, that they had neither the skilled surgeons nor the equipment to deal with those major military and civilian injuries which came under the aegis of the orthopædic division of the E.M.S. It was then that Tom Fairbank's gentleness and humble mindedness were seen to disarm all opposition and reconcile conflicting interests. Throughout my long and close friendship with him I never heard him utter an unkind criticism of the work or personality of any colleague."

At the end of the war he was 69 and he might have retired from active work, but he returned to his consulting practice and for several years more did some hospital work. But he found increasing deafness a growing handicap, and in 1948 he closed down his work at Harley Street and soon afterwards with Lady Fairbank set out on a long visit to his daughter in New Zealand, and on the journey he made contacts with orthopædic surgeons wherever he went. Back in London he settled to work on his great collection of material on skeletal disorders. A series of important articles and lectures on diseases of bone culminated in the publication in 1951 of his *Atlas of General Affections of the Skeleton*.

N. C., to whom we are indebted for this memoir, adds the following personal tribute:

"In the war Fairbank was not content to work from an office; he spent much time touring the country units seeing at first hand the problems of even the most junior consultants. His memory for names and places was remarkable and his official visits were times of great intellectual refreshment for us. Though he always seemed tireless, he clearly over-worked himself during these years. It is strange how the lessons of war are forgotten so soon afterwards. Now we are thinking of organising accident services on the idea of central and peripheral satellite units. This Fairbank did in the E.M.S., when he instituted central A and B fracture departments.

"Whatever he wrote was illuminated by wide reading of the literature: he was most punctilious in his acknowledgment of sources as indeed he was generous to those who provided him with material. He was a constant visitor to the library of the Royal Society of Medicine, and the sight of his wonderful head will be missed there. Although Tom Fairbank reached a great age, he never seemed to us an old man. He well exemplified the words of Cicero: 'the studies which were an impetus to his youth do now in age provide his delight'."

Sir Thomas married in 1909 Miss Florence Kathleen Ogilvie, who survives him. They had two daughters and a son, who is orthopædic surgeon to the United Cambridge Hospitals.

THOMAS RENTON ELLIOTT

C.B.E., D.S.O., M.A., M.D. Cantab., F.R.C.P., F.R.S.

Prof. T. R. Elliott, who died on March 4, was the first director of the medical professorial unit at University College Hospital. As a scientist, administrator, and teacher he was a man of great influence, whose wisdom did much for medicine in this country.

He was born in 1877, the son of A. W. Elliott of Willington in Co. Durham, and was educated at Durham School and Trinity College, Cambridge. He took a double first in the natural sciences tripos and he is also remembered from undergraduate days as a rugby-football player and a rifle shot. Thereafter he spent about eight years in Cambridge working at the physiological institute while holding college and university studentships. Of this productive period H. H. D. writes:

"It was during his tenure of postgraduate stipends that Elliott carried out nearly the whole of those brilliant researches which will surely keep his name alive in the history of physiological discovery. Following the traditions of the Cambridge School at that time, he carried further the study of the autonomic nervous control of the involuntary bodily functions—those of the circulatory system, abdominal viscera, bladder, and urethra—and especially of the then still mysterious correspondence between the effects on such functions of impulses in the nerves of the 'true' sympathetic system, and those, on the other hand, produced by injection or application of the then recently isolated adrenaline. His comprehensive findings in this field happened to make contact with some which I myself was then encountering; and it seemed to me then, as it seems to me still, whenever I look at them again, that the great series of papers in which Elliott presented his observations and his ideas in the *Journal of Physiology* between 1902 and 1907, were of a well-nigh incomparable brilliance and authority, for a worker still so young in years and experience. As early as 1904 he put forward, in a note giving the gist of a communication to the Physiological Society, the first clear and specific suggestion of a chemical transmission of the effects of nerve impulses, from the nerve endings to the continuous cells of effector organs; a conception which, then years before its time, has in relatively recent years acquired, of course, a much wider and still extending significance, in experimental physiology and pharmacology, and now in clinical medicine.

"Many, I believe, have found it difficult to understand the fact that Elliott's directly personal engagement in experimental research, in physiology, or, indeed, in any part of the medical field, seemed, after so brilliant a beginning in Cambridge, to have come permanently to an end, with his removal to University College Hospital, to complete his medical course and to hold the appointments leading to a clinical career. I had less feeling of surprise, though still some of regret, at this change;

for I knew that it had not been due just to the pressure of other demands, or to any lack of a fresh initiative. He had told me, indeed, of his own firm conclusion, that he would, thenceforward, be able to do his best service to medicine, in promoting its development into an experimental discipline, by putting all his energy and the weight of his influence into teaching, encouragement, and organisation of opportunity for others; and I am content to believe that his decision was the right one."

G. G. describes another side of these years:

"I knew T. R. Elliott when he was in his fourth or fifth year at Trinity, and I was a fresher. I got to know him because he was a colour-sergeant of E Company (Trinity) in the Cambridge University Volunteer Rifles and I was a private. I was in his tent at Aldershot and he looked after us very well. His knowledge of squad drill was considerable and E Company won the London Scottish Cup for squad drill two years running and also the Wale Plate for shooting after a ten-mile march carrying full equipment. Having got to know him so well in camp, he was always approachable at Cambridge and often gave me good advice. At that time he was working on the adrenal glands and I was thrilled, one night, to be asked after hall to help him in the physiology laboratory with an adrenalectomy on a cat."

When Elliott went to University College Hospital in 1906 as a medical student he was thus already renowned as a physiologist.

In his final year at U.C.H. he shared lodgings with Thomas Lewis in Mornington Place, "when the Crescent held a shrubbery and not Carreras' factory, and where all the passing trains of what was then the Midland Railway vomited smoke and spat ashes at us. There we worked together in our common sitting-room in the evenings, and dined in it monotonously on what passed for boiled mutton and parsley sauce."

The rest of Elliott's career was centred on U.C.H. After qualifying he held house-appointments and a Beit fellowship, and before his work was interrupted by the 1914–18 war he had already been elected F.R.S. and was a member of the staff. The next years he spent in France, at first as assistant to his old chief Rose Bradford.

From the very beginning of the new Medical Research Committee (later Council) he had been in the counsels of those responsible for it—especially after another Trinity friend, the late Sir Walter Fletcher, was appointed its first secretary. As consulting physician to the Forces in France, Elliott became the chief contact for the Committee, and the trusted adviser to Fletcher, on the reorientation of medical researches to the needs of war. For his work on gunshot wounds he was awarded the D.S.O. and appointed C.B.E.

He returned to U.C.H. to become director of one of the new professorial units which had been set up at his school. In an appointment that was an opportunity as well as a challenge he soon showed that he was as brilliant an administrator as he was research-worker and clinician. With Sir George Blacker he attracted munificent Rockefeller endowments to the school and hospital. Of his own characteristic contribution, M. R. relates:

"When the Rockefeller Foundation made a special gift to the hospital for the maintenance of the medical and surgical beds, it was Elliott who inserted a simple clause to the effect that, should the Government at any time assume charge of hospital beds, that capital sum should pass to the Medical School for research. This was a remarkable piece of foresight, the benefits of which we enjoy today and which will be appreciated for years to come.

"T. R. Elliott, Thomas Lewis, and Wilfred Trotter were the giants of U.C.H. in the days between the wars, and each, in his own way, has left an indelible mark. While Thomas Lewis was widening the scope of clinical science, Elliott was shaping the future of academic medicine in this country, and the many whole-time professorial units in our medical schools today owe much to his guidance and sagacity. It is a great privilege to have been his house-physician, to have seen his eager and critical mind at work, to have listened to his forthright but kindly teaching, and to have learnt clinical medicine from a real master."

After Elliott retired from his unit in 1939 he continued his work for the Medical Research Council and as medical adviser to the Beit Memorial Trust. As one of the first trustees appointed under Sir Henry Wellcome's will, he joined forces again with his old friend Sir Henry Dale in an exciting and valuable contribution to medicine. But growing disability finally led him to retire permanently to the house which he and his wife had built in Scotland, and where he died. Speaking of the "undemanding friendship on which many of us had learned to depend", Sir Henry sums up his public achievement as one of "inestimable value to the progress of medical science".

W. R. T. sends a tribute from a younger generation:

"Elliott's most outstanding characteristic was his robust and vigorous commonsense. His high scientific reputation, and outstanding ability as a practising physician, obtained him the directorship of one of the original professorial units to be established in London. But he would have been far less successful in that key position if it had not been obvious to his colleagues that he was not a man to be carried away by fanciful notions. It was a time when the first tentative essays were being made in the application of scientific methods to clinical problems; and when, for the first time, a serious attempt was being made to teach medicine as an academic discipline. Both these new ventures were regarded with intense suspicion by most clinicians. Elliott's practical and down-to-earth approach to problems as they arose was reassuring and did more than anything to ensure the prospects of his new unit. This was the most successful of the professorial units established in London teaching hospitals after the first world war. Unlike most of the others, there were never any doubts about its success and viability, and it soon became a model of its kind to be imitated elsewhere. The great achievement of the later phase of Elliott's life was the practical demonstration that an academic unit, combining teaching, research and the care of patients, could actually be made to work.

"During nearly all his time as director, Elliott was plagued by a particularly obstinate sciatic pain which forced him to install a couch in his room, from which the unit's activities were largely directed. This curtailed his physical activities a good deal, and forced him to abandon his own personal research work. But he soon proved adept at selecting and training a stream of young men who went out to posts, at U.C.H. and elsewhere, imbued with Elliott's ideas and inspiration. He taught them to deal with the symptoms and signs of disease as the raw material of a scientific discipline, to be observed, measured, and argued about as the starting point for fresh investigations. The generation he trained has succeeded in establishing this point of view, and we are now seeing the fruits of the application of scientific methods to clinical problems.

"Elliott's teaching was simple, direct, and heavily laced with commonsense. He distrusted alike abstruse diagnosis and complicated treatment. He was always willing to discuss new theories, but to gain his interest they had to be simple and to lead to practical conclusions which could be tested. Moreover he was always genial, kind, and readily approached by the young. Perhaps the greatest of his virtues, in a more dogmatic climate than now prevails, was his instant readiness to admit that he did not know."

Professor Elliott married in 1918 Martha, daughter of A. K. M'Cosh of Airdrie. There are three sons and two daughters of the marriage.

Notes and News

DENTISTS' REMUNERATION

LAST Saturday the British Dental Association accepted on behalf of its members and other dentists in the country the "package deal" offered by the Ministry of Health. There was some reluctance to make this decision, because about a fifth of the Association's members had voted against it. A smaller and more combative organisation, the General Dental Practitioners Association, is still unreconciled.

The pay recommendations will affect about 11,000 dentists practising in the National Health Service, and are based on the findings of the Royal Commission on Doctors' and Dentists' Remunerations.

Though the settlement does not offer any definite promise of an increase in dentists' earnings, it does safeguard the profession from any cut by the Minister of Health in the rates paid for N.H.S. work. In addition, a Dental Rates Study Group is to be set up to review N.H.S. fees paid to the practitioner, and to ensure that his average net earnings are roughly £2500 a year. Hospital dentists are to be placed on a parity with hospital doctors and will receive increases in remuneration.

Much of the criticism levelled at the "package deal" is based on its continuance of the present system of itemised payments which many feel is a far from ideal basis of remuneration for either the operator or the patient.

GUY'S HOSPITAL DENTAL SCHOOL

THE annual clinical meeting of the Guy's Hospital Dental School on March 4 had no major advances to record since the last meeting, but many things which were novelties a short time ago—such as the airotor, which was still attracting considerable attention even last year—have now become an accepted part of dental practice.

Mr. W. J. Tulley, of the children's department, showed an interesting film on the long-term effects of orthodontic treatment. Mr. Tulley has been fortunate enough to be able to follow up some of his patients for as long as fifteen years, and this film, which is to have a sound-track added for teaching, shows what can (and cannot) be expected of modern orthodontics.

The main lecture of the day, on surgical emergencies in everyday practice, was given by a guest Mr. B. W. Fickling, from the Royal Dental Hospital. He dealt with a number of incidents, such as displaced teeth, teeth forced into the maxillary sinus, and troublesome hæmorrhage, which, though they can be treated in the dental surgery, may cause some anxiety unless the surgeon has a definite plan of action.

A predecessor of the airotor—the ultrasonic unit—has now reappeared as a means for scaling and gum treatment. In its new role the instrument seems very efficient, and minor gingivectomies are possible without anæsthesia. At present, the ultrasonic unit has to be imported and its high cost (about £300) is likely to limit its use.

There was the usual packed lecture-theatre for Prof. M. A. Rushton's lecture on interesting cases referred to him during the year. Two unusual dental manifestations of systemic disease have recently been noted in his department. Children with fibrocystic disease of the pancreas (mucoviscidosis) have dental enamel of a peculiar bluish translucency. The appearance is pathognomic but careful examination of extracted teeth, both in this country and also in the United States, has failed to show any structural changes. The nature of the pigment has not yet been determined. Icterus neonatorum causes horizontal bands of orange pigmentation in the enamel, often associated with hypoplasia, at the level of the stage of calcification at birth.

Mr. R. D. Emslie and his colleagues from the department of preventive dentistry have been investigating the possibility of giving fluoride in specially prepared chewing gum. Preliminary results [1] show that children's teeth will absorb theoretically adequate amounts of fluoride from this gum. The trial has not yet been conducted for long enough to decide whether there is any reduction in the incidence of caries.

1. Emslie, R. D., Veall, N., Duckworth, R. *Brit. dent. J.* 1961, **110**, 121.

University of Cambridge

On Feb. 25 the degrees of M.B., B.CHIR. were conferred on G. D. Ingram by proxy.

University of London

Dr. Desmond Curran, senior psychiatrist at St. George's Hospital, has been appointed to the chair of psychiatry at St. George's Hospital Medical School.

Dr. Curran, who is 58 years of age, was educated at Wellington College, at Trinity College, Cambridge, and at St. George's Hospital. After qualifying in 1927 he held resident appointments at the Maudsley Hospital and the Maida Vale Hospital. In 1930 he was awarded a Rockefeller fellowship and spent a year in Baltimore as assistant psychiatrist at the Phipps Clinic of the Johns Hopkins Hospital. He was appointed to the staff at St. George's in 1933, and he was awarded the Gaskell Gold Medal in the same year. He was elected F.R.C.P. in 1937. During the late war he was consultant in psychological medicine to the Royal Navy and since 1946 he has been civil consultant to the Service. In 1948 he delivered the Croonian lectures to the Royal College of Physicians on prefrontal leucotomy, and he is joint author of a textbook on *Psychological Medicine*.

Dr. Cyril Long, head of the biochemistry division at the Institute of Basic Medical Sciences, has been appointed to the university readership in biochemistry at the Institute.

University of Birmingham

The title of reader in neuropharmacology has been conferred on Dr. P. B. Bradley, the title of first assistant to the chair of pathology on Dr. D. B. Brewer, and the title of university clinical lecturer in surgery on Mr. K. D. Roberts.

University of Dublin

The Senate has granted graces for the degree of LL.D. to be conferred on Major-General H. E. Knott, at present deputy director-general of Army Medical Services.

At a commencement to be held in September during the meeting in Dublin of the International Surgical Society, the degree of M.CH. will be conferred on Prof. Charles Rob, of Rochester, New York.

Royal College of Obstetricians and Gynæcologists

On March 15 Mr. R. G. Menzies, the Prime Minister of Australia, will be admitted to the honorary fellowship when he visits the college.

On Friday, March 24, at the college, 27, Sussex Place, Regent's Park, London, N.W.1, there is to be a scientific meeting on the recognition and treatment of fœtal abnormality.

Association of Clinical Biochemists

Southern England and South Wales Region.—On Thursday, March 16, at 7.30 P.M., at the Royal Free Hospital Medical School, Hunter Street, London, W.C.1, Prof. H. B. Collier will give a lecture on recent advances in red-cell chemistry.

International Course in Ophthalmology

The third international course of the Instituto Barraquer will take place from May 1 to 5 in Barcelona. The programme will include a symposium on the surgery of the crystalline lens with reference to the use of intraocular plastic lenses and a symposium on the surgery of the cornea including corneal grafts. Further particulars may be had from Sir Benjamin Rycroft, 35, Harley Street, London, W.1.

Committee on Central Sterile Supply Departments

The Central and Scottish Health Services Councils have appointed a committee to consider the policy which should be followed on the provision of central sterile supply services in National Health Service hospitals and the organisation and control of central sterile supply departments. The members are:

E. F. Collingwood, D.SC. (chairman), Sir Stanford Cade, F.R.C.S., J. Constable, A.M.I.C.E., P. H. Constable, F.H.A., E. M. Darmady, F.R.C.P., Prof. A. S. Duncan, F.R.C.O.G., H. Grainger, F.P.S., W. J. B. Groves, F.H.A., Prof. E. A. Pask, F.F.A. R.C.S., J. Revans, M.R.C.S., E. K. Samways, F.P.S., Miss T. Turner, S.R.N., appointed by the Central Health Services Council; G. R. Milne, F.P.S., Prof. J. W. Howie, M.D., Cameron Weymes, appointed by the Scottish Health Services Council; the secretary is Mr. E. L. Wallis, Ministry of Health, Savile Row, W.1.

Christian Medical Fellowship

On Wednesday, March 15, at 8.15 P.M., at a meeting of the fellowship at the Royal Commonwealth Society, Northumberland Avenue, London, W.C.2, Mr. W. Melville Capper will speak. The title of his discourse will be Questions Colleagues Have Asked Me.

Association Européenne du Corps de Santé

This association, which is being formed by doctors interested in European affairs and particularly in the problems of European unity, is meeting in Paris on March 18 and 19 and hopes to hold a congress on Nov. 3, 4, and 5. British doctors who are interested are asked to write to the Administrative Secretary, 45, Rue d'Hauteville, Paris, 10e.

Association of Industrial Medical Officers

A meeting of this Association will take place on Friday and Saturday, March 24 and 25, at the London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1, and the Maudsley Hospital, Denmark Hill, London, S.E.5. Further particulars may be had from the hon. secretary of the Association, 47, Lincoln's Inn Fields, London, W.C.2.

Bristol Industrial Therapy Organisation

On Feb. 27 (*Times*, Feb. 28) Sir William Grant, the chairman of the board of this organisation, announced that the Nuffield Provincial Hospitals Trust has made a grant of £3500 over the next three years to help to start a workshop which would give permanent jobs at a guaranteed minimum wage of £6 a week to some twenty psychiatric patients not able to compete in open employment. The organisation's half-way factory for patients who hope to return to work in the community has been described in our columns (*Lancet*, 1960, ii, 754).

National Association for Mental Health

A residential weekend course on psychiatry for the general practitioner is to be held by this Association from May 5 to 7 at the Kenilworth Hotel, Great Russell Street, London, W.C.1. This course is recognised by the British Postgraduate Medical Federation under the Ministry of Health postgraduate scheme for general practitioners. The cost of the course, including residence and tuition, is £2 12*s*. 6*d*. Application forms may be had from the education secretary of the Association, 39, Queen Anne Street, London, W.1.

British Occupational Hygiene Society

On Tuesday, April 11, at Birkbeck College, Malet Street, London, W.C.1, this society is to hold a conference to consider the need for industrial hygienists in industry and the type of training facilities which can be provided. The speakers will include Dr. J. M. Rogan, Dr. A. Lloyd Potter, Dr. E. H. Capel, Dr. D. E. Hickish, Dr. G. J. Fortuin, Dr. C. H. Wood, Prof. R. E. Lane, and Prof. R. C. Browne. Non-members of the society will be welcome. Application for registration (21*s*.) should be made to Mr. J. Steel, department of industrial health, Medical School, King's College, Newcastle upon Tyne.

The National Fund for Research into Poliomyelitis and other Crippling Diseases

This fund has announced grants totalling nearly £60,000. They include the following:

£10,500 to the Nuffield Orthopædic Centre, Oxford, to finance development of aids for the upper limb; £6255 to the department of medicine, University of Sheffield, for its work in virology; £5660 to the department of bacteriology, University College Hospital Medical School, to establish a research fellowship in virology; £18,000 to the Christian Medical College and Hospital, Vellore, South India, to help in enlarging and equipping the department of physical medicine; £11,000 to the department of microbiology, Queen's University of Belfast, for veterinary and other studies on poliomyelitis.

Sir Benjamin Rycroft will be a guest speaker at the Eye Surgery Clinical Meeting which is held at the University of Toronto from March 20 to 22. His subjects will include corneoplastic surgery, the surgery of the lacrimal apparatus, and keratoplasty.

The annual general meeting of the Anglo-American Medical Society will take place on Wednesday, March 22, at 8.30 P.M., at the Cambridge University department of biochemistry, Tennis Court Road, Cambridge.

Diary of the Week

MARCH 12 TO 18

Monday, 13th

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Major-General Robert Drew: Rickettsial Diseases.

Tuesday, 14th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Experimental Medicine and Therapeutics*. Prof. D. H. Smyth: Absorption from the Intestine. Dr. Edith Bülbring: Motility of the Intestine.
8 P.M. *Psychiatry*. Sir Robert Platt, Dr. Denis Hill (representing U.K.), Dr. Ralph Kaufman, Dr. Lawrence E. Hinkle (representing U.S.A.): Place of Psychiatry in Medicine Today.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
3 P.M. (Hammersmith Hospital, Ducane Road, W.12.) Prof. Lee Buxton (Yale): Investigation and Treatment of Irregular and Profuse Menstruation and Abnormalities of Ovulation. (Third of six lectures.)

ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. (Wright-Fleming Institute.) Mr. Aleck Bourne: Gynæcology of Old Age.

BIRMINGHAM MEDICAL INSTITUTE, 36, Harborne Road, Edgbaston
8 P.M. *Psychiatry*. Prof. F. Lafitte: Family Planning.

UNIVERSITY OF LIVERPOOL
5.15 P.M. (114, Mount Pleasant, Liverpool.) Mr. Hugh Reid: Life and Times of Andreas Vesalius.

MANCHESTER MEDICAL SOCIETY
8 P.M. (Clinical Sciences Building, York Place.) *Surgery*. Mr. F. G. Ralphs: Gastrointestinal Granuloma. Mr. N. F. Kirkman: Acute Appendicitis.

Wednesday, 15th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
4 P.M. Dr. R. P. W. Shackleton: In my End is my Beginning. (Frederic Hewitt lecture.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. J. F. A. McManus: Essential Renal Lesion of Chronic Pyelonephritis.

ROYAL SOCIETY OF MEDICINE
5 P.M. *Comparative Medicine*. Prof. A. S. Parkes, Dr. Margaret Hadley Jackson, Dr. G. E. Lamming: Hormonal Control of Fertility in Man and Animals.
8.15 P.M. *General Practice*. Dr. John Hunt, Dr. T. F. Fox, Dr. George A. Silver (New York): General Practice in a Changing World.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Henry Haber: Dyskeratosis.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. I. S. Longmuir: Effect of Temperature on Diffusion and Chemical Kinetics in Biological Systems.

ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.15 P.M. Prof. Jean Hamburger (Paris): Renal Transplantation.

HARVEIAN SOCIETY OF LONDON, 11, Chandos Street, W.1
8.15 P.M. Sir Zachary Cope: My Medical Case Book for 1905. (Harveian lecture.)

Thursday, 16th

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W.1
8 P.M. Dr. Gilbert Fletcher, Mr. G. W. Blomfield: Treatment of Carcinoma of the Cervix by Super-voltage Radiation.

WEST LONDON MEDICO-CHIRURGICAL SOCIETY, West London Hospital, Hammersmith, W.6
7.30 P.M. Mr. Edward Wrangham: Sola Khumbu Expedition.

MANCHESTER MEDICAL SOCIETY
8 P.M. (Staff House, University of Manchester.) *Anæsthetics*. Dr. F. L. Robertshaw: Hypothermia for Cardiac Surgery.

Friday, 17th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. L. P. Le Quesne: Pyloric Stenosis.
4 P.M. Dr. Wallace Brigden: Pericarditis.

ROYAL SOCIETY OF MEDICINE
2.30 P.M. *Experimental Medicine and Therapeutics*. (Jointly with the Renal Association.) Prof. A. R. Rich (Baltimore), Dr. R. L. Vernier (Copenhagen), Professor Hamburger, Dr. C. Brun (Copenhagen), Prof. D. P. Earle (Chicago), Prof. R. Kark (Chicago): Discussion on the proceedings of the Ciba Foundation Symposium on clinico-pathological significance of renal biopsy.
5.30 P.M. *Epidemiology and Preventive Medicine*. Dr. J. O. F. Davies: Problems for Operational Research in the National Health Service.
8.15 P.M. *Radiology*. Dr. Frank Ellis: Recent Radiobiology and the Radiotherapist. (Presidential address.)

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Mr. Kenneth McLay: Sinusitis.

INSTITUTE OF OBSTETRICS AND GYNÆCOLOGY
4.30 P.M. (Chelsea Hospital for Women, Dovehouse Street, S.W.3.) Professor Buxton: Investigation of the Infertile Couple. (Fourth of six lectures.)

UNIVERSITY OF LIVERPOOL
5.15 P.M. (New Medical School.) Mr. B. N. Brooke: Development of Blood-transfusion.

Appointments

BEARD, A. W., B.M. Oxon., M.B. Cantab., M.R.C.P., D.P.M.: consultant physician in psychological medicine, Middlesex Hospital, London.
JONES, C. T., M.R.C.S., D.P.H., D.I.H. M.O.H., King's Lynn and Freebridge Lynn, and M.O., King's Lynn port health authority.
MORRISON, H. R., M.B. St. And., D.P.H.: M.O.H., Richmond, Yorkshire.

The Hospital for Sick Children, Great Ormond Street:

BANDARANAIKE, S. R. DIAS, M.A., M.B.: house-physician.
CAIN, A. R. R., B.M. Oxon., D.OBST.: house-physician.
FENNELL, G., L.R.C.P.I., D.L.O.: senior registrar, E.N.T. department.
JEFFERIES, J. D., M.B. Brist.: house-surgeon.